

















**National Institutes of Health (U.S.)**

**Office of the Director**

**SPEECHES, ARTICLES, AND SELECTED PAPERS**

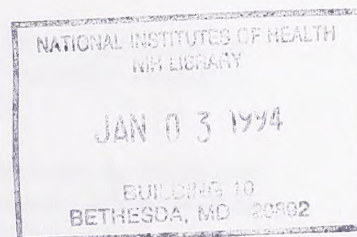
**By**

**James B. Wyngaarden, M.D.**

**1982-1988**

**Volume 5 (of 5)**

**(November 16, 1987—July 24, 1989)**





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**Speeches, Articles, and Selected Papers**  
**James B. Wyngaarden, M.D.**

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# BIOMEDICAL RESEARCH POLICY FOR THE 21ST CENTURY\*

by

James B. Wyngaarden, M.D.\*\*

Just over five years ago it was my pleasure and privilege to give the keynote address at the first Research Day observed by the University of Kansas Medical Center. That was in the fall of 1982, not long after I was appointed Director of the National Institutes of Health, after having served as a member of the faculty of an academic health center for most of my career prior to that time. Consequently today brings back to me the special feeling that comes from associating with able and highly motivated young men and women.

My subject today, however, is not the past but the future for which today's training, academic preparation and research investigation is the essential prelude. In planning for my talk it seemed appropriate to the occasion to express some thoughts on biomedical research policies and their possible effect on the late 20th and early 21st centuries.

During the past year the National Institutes of Health has been observing the 100th anniversary of its establishment. In the course of that observance, my colleagues and I have made a substantial number of speeches about the interesting history of medical science since 1887. In today's talk I will not dwell on that history, but in order to discuss our outlook for the future it will be useful for me to relate some of the events of the past to the current situation, and from that to venture some ideas regarding the future.

One of the themes we have stressed during the NIH's year-long centennial observance is the importance of the partnership among government, academia and industry in long-term efforts to improve the

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\*Keynote address presented at the Faculty Research Day,  
University of Kansas, Kansas City, Kansas, November 16, 1987.

\*\*Director, National Institutes of Health, Bethesda, Maryland



health of the American people through biomedical research and the application of its fruits.

#### Biomedical Research as a Federal Activity

But it was not until after World War II that collaboration between the Federal Government and academic institutions for the conduct of biomedical research was considered as an appropriate object for expenditure of Federal funds. It was then that our extramural programs began. Since that time the NIH programs have exercised a powerful influence on public and private American universities. The cumulative effect has been particularly marked in the area of the biological sciences and in the academic medical centers. The substantial and increasing funding through NIH of research conducted at universities and academic health centers has permitted appointments of additional faculty oriented toward research. Furthermore, many scientists trained in the intramural research programs of the NIH have become senior faculty members and administrators in both basic and clinical research institutions.

When, in late 1944, it began to appear that the war could be brought to a successful conclusion, President Franklin D. Roosevelt addressed a letter to the Director of the Office of Scientific Research and Development, Dr. Vannevar Bush, and asked his recommendations on four major points. The first was on the question of how scientific knowledge gained during the war could safely be diffused for the improvement of the national well-being. This question might at first seem strange, but it was wartime and much scientific activity was classified.

His second question concerned the war of science against disease. The answer to this question became highly significant in the development of the National Institutes of Health. The President asked what could be done to organize a program for continuing in the future the work that had been done in medicine and related sciences.

The third question came right to the point. Roosevelt asked, "What can the Government do now and in the future to aid research activities by public and private organizations?"<sup>1</sup>

Finally the question was asked "Can an effective program be proposed for discovering and developing scientific talent in American youth so that the continuing future of scientific research in this country may be assured on a level comparable to what has been done during the war?"<sup>1</sup>

Vannevar Bush responded with a report that is a basic statement of Federal science policy. One of his responses contained a classic description of the role of academic institutions in research. He noted that, "The publicly and privately supported colleges, universities and research institutes are the centers of basic research. They are the wellsprings of knowledge and understanding. As long as they are vigorous and healthy, and their scientists are free to pursue the truth wherever it may lead, there will be a flow of new scientific knowledge to those who can apply it in government, in industry, and elsewhere."<sup>2</sup>

During the war years essentially all of the American scientific community had been mobilized to serve military needs. Grants and contracts were awarded to American academic institutions, hospitals, and independent laboratories for the conduct of research on health problems expected to be encountered by members of the armed services. Something over 500 grants and contracts for medical research were awarded during the war years. About 250 awards were still active when the Office of Scientific Research and Development was disbanded in 1945. The ongoing projects were turned over to the NIH for administration.

That was a turning point in our history. The action had a twofold meaning. It meant that for the first time approval was given to Federal support for biomedical research in non-government laboratories during peacetime. Further, the action in effect designated the NIH as the principal biomedical research arm of the Federal Government.

The post World War II period in the United States was a time of ebullient confidence that our Nation could accomplish any task, no matter how difficult, if it decided to do so. This climate of optimism was channeled by leaders in science and medicine as a driving force for the establishment of the modern NIH.



### Extramural Research--The Federal-Academic Partnership

No patterns existed for administering our extramural grant program, but in little more than a year after the passage of the authorizing legislation a system was put in place that has stood the test of time and serves as a model for granting organizations.

The system was built on the basic tenet that it should protect the integrity and the independence of the research worker and his freedom from control, direction, regimentation and outside interference. It mandated the selection in open competition of projects to be supported, relying heavily on the appraisals of non-Federal scientists. In this manner the system was designed to use the expertise of scientists throughout the Nation, both in the conception and conduct of the research and in the evaluation of research proposals.

Two generations of research investigators and health practitioners have been the beneficiaries of the farsighted efforts and plans of leaders such as Vannevar Bush. Their influence seems certain to persist well into the 21st century. These scientist-statesmen have convinced policy makers in the United States of the necessity of taking a long-range view of science--of the need to invest in fundamental research without regard to when or even whether it might lead to useful discovery. This mature view of the need for continued basic research bodes well for the future of science, but more importantly it will be the key to improvements in the health and well-being of the American people.

### The Federal Government's Role in Basic Research

Twenty years after Vannevar Bush recommended a national policy accepting research as a Federal activity, another description of the philosophy underlying the science and technology policy of the United States appeared in a report called "Basic Science and the National Goals." The report was made to the Committee on Science and Astronautics of the U.S. House of Representatives. Professor Harvey Brooks of Harvard wrote about the functions of basic research as a government activity. Among these functions he spoke of the cultural, social, economic and educational significance of such fundamental research.

With regard to the cultural role of basic research, he said, "....(it) is recognized as one of the characteristic expressions of the highest aspirations of modern man. It bears much the same relationship to contemporary civilization that the great artistic and philosophical creations of the Greeks did to theirs, or the great cathedrals did to medieval Europe. In a certain sense it not only serves the purposes of our society, but IS one of the purposes of our society."<sup>3</sup>

Regarding the economic dimension of basic research, Dr. Brooks noted that "there is now a general acceptance among economists of the importance of technical innovation in economic growth. To an increasing extent, he said, "Such innovation depends upon the results of basic science."<sup>3</sup>

As to the social significance of basic research, he pointed out that there is a recognized Federal responsibility for public health, and that in this area the Federal Government has been quick to utilize research in support of its mission, including a substantial amount of basic research.

His final comment was upon basic research and education. In this connection, Dr. Brooks spoke of how in recent years the intimate connection between the two has been emphasized. He reminded the Congress, however, that in engineering, medicine, agriculture and several other areas, applied research is equally as important as advanced training. He mentioned that the healthy flow between basic and applied science has been one of the characteristics of American science contributing to its vitality.

Just three years ago the President's Science Advisor George Keyworth, following a review of Federal science policy, reported that perhaps the most important element of policy that emerged from recent reassessments was a renewed and considerably strengthened Federal support for basic research. "Quite simply," he said, "basic research is a vital underpinning for our national wellbeing."<sup>4</sup>

And early this year, when President Reagan presented his budget estimates for Fiscal Year 1988, the Office of Management and Budget prepared and transmitted to the Congress a special analysis of the budget.



Once again the Government's role with regard to research was stated. Permit me to quote from the document:

"The Federal Government supports research and development to assist in meeting broad national needs, particularly where the private sector lacks sufficient incentives for adequate investment to assure long term economic growth and continued improvement in the quality of life for all citizens. Examples of such research and development include Federal investments in basic research across the fields of science and engineering, and agricultural and health-related research and development."<sup>5</sup>

The document made the case for research in the 1988 budget not only to meet current and foreseeable national needs, but also on grounds of immediate interest to academic and scientific institutions. Special mention was made that the budget provided for, "...basic research, particularly at universities to help generate the new knowledge necessary for continued technological innovation and to secure the future availability of high quality scientists and engineers."<sup>5</sup>

Over 60 percent of all the research supported by the National Institutes of Health is basic research, conducted in order to increase our understanding of living systems, and without a specific application in mind at the time. I want to stress how important I think it is that we continue to devote adequate resources to basic research.

The total budget of the NIH in Fiscal Year 1987 was over \$6 billion. That represents a 70 percent increase in just the past five years. Currently well over 80 percent of the NIH budget is devoted to support of research through grants and contracts awarded to about 1650 academic institutions, hospitals and other laboratories. More than 50,000 scientists perform research supported by the NIH through the extramural programs.

#### Recruitment and Retention of Scientific Talent

Future availability of high quality scientists is the essential issue in any appraisal of the future of biomedical research in the 21st century. And more than 40 years ago this point was underlined in President Roosevelt's

request for advice on an effective program for discovering and developing scientific talent so that the continuing future of research can be assured.

As a part of his response to the President, Vannevar Bush quoted a statement from Harvard President James B. Conant that is fully as applicable to today's situation as it was during World War II. Dr. Conant stated that "...in every section of the entire area where the word science may properly be applied, the limiting factor is a human one. We shall have rapid or slow advance in this direction or in that depending on the number of really first-class men who are engaged in the work in question....So in the last analysis, the future of science in this country will be determined by our basic educational policy."<sup>6</sup>

From these concerns came new and highly effective programs that had a direct effect on the training of scientists in this country, for example, the GI Bill, the establishment of the National Science Foundation and the extramural programs of the National Institutes of Health. These and other programs served well the subsequent development of science in the United States. But the requirements of such a dynamic enterprise as science cannot be provided for once and for all, and it is our special responsibility as scientists and administrators to give urgent attention to the future supply of trained scientists.

A consequence of the amazing progress that has been made by the current generation of scientists is the level of sophistication required of their successors if progress is to be continued. In the biological sciences there has also been a substantial broadening of the scope of research. We have totally new disciplines within the biosciences so that larger numbers of more highly trained investigators will be needed if we are to continue the pursuit of discovery in new areas, such as structural biology and molecular genetics.

The Government-University-Industry Research Roundtable, of the National Academy of Sciences, has been encouraging widespread discussion of the issues relating to the development, identification, recruitment and retention of science and engineering talent.



In evaluating the status of the talent pool, a working group of the Roundtable predicts that the demand for scientists and engineers will remain strong in both industry and academia, but that at the same time the number of Americans qualified for these careers may be declining.

This prediction is based in part on certain disturbing trends. First, the supply of 22-year-olds is projected to drop more than 25 percent before the end of the century. If even the current level of supply for industry and academia is to be maintained, a significant increase in the proportion of 22-year-olds attaining science and engineering degrees will be necessary. The Roundtable group estimated that to maintain the 1985 level into the 1990s, the degree award rate would have to increase by 30 percent.

A special problem is posed by indications of shortages of competent science and mathematics teachers in secondary schools, and with the evidence of the lack of achievement of U.S. students in mathematics. This has serious implications in the biosciences as well as in engineering.

Although the awards of Ph.D.s in the life sciences are up, a substantial drop in the number of baccalaureate degrees in the life sciences that began in the late 1970s continues unabated and portends shortages.

There has been a linear decline in interest in careers in these fields on the part of the traditional performers (young males), and although the number of women and minorities is on the increase their numbers do not make up for the losses. The number of women enrolling in and graduating from medical school continues to rise, although the number applying has declined. All applications to U.S. medical schools declined for the 1986-1987 academic year, and according to a report issued in August of this year, first-time enrollments fell for the fifth year in a row.

Given the demographics of the last decade of the 20th century, it is abundantly clear that if the necessary talent is to be available for continuation and extension of the explosive progress in the biological

sciences, we must attract a greater share of young people into those fields.

Serious attention must be given to finding ways to develop the interests and abilities of children in grade school. The early years are critical.

Secondary school is the period when decisions can begin and the choices made in high school courses become crucial with respect to future careers.

The undergraduate years take a heavy toll in the numbers of students who elect to pursue careers in the sciences. When the time comes to decide whether or not to go into graduate or professional school, we have to recognize that a decisive factor is the student's perception of career opportunity, versus the investment in time and dollars required to prepare for such a career.

Because the NIH is the source of funding for almost two-thirds of the biomedical research conducted in American universities, our programs are influential and also are regarded as indicators of activity and opportunity. For this reason we have stressed to the administration and the Congress the importance of stable funding, particularly of our project research grants. A reasonable degree of predictability of research support is essential for institutions and for individual investigators if they are to attract and maintain productive teams of researchers. Furthermore, such stability can indicate to young people at critical stages in their careers that there is reasonable assurance that, having completed the intensive training that today's science requires, they will be able to look forward to active careers in health-related research.

The maintenance of our Nation's scientific leadership in this vital field requires a continuous infusion of well trained, highly motivated young scientists. It goes without saying that it is our purpose at the NIH to administer the extramural programs in such a way as to inspire confidence.



This is important to the long-range future of science, and it is also of current concern. For the grant programs of the NIH, particularly that part devoted to investigator- initiated projects draws upon the expertise and the intuition of practically the entire American scientific community. In recent years the number and quality of research proposals have increased steadily and have outstripped our ability to fund them, even though the NIH budget has continued to grow in real terms by 2 percent per year since 1965, and 5-6 percent per year in the past 5 years.

We now find ourselves having to turn down more and more applications that a few years ago would certainly have been funded. At this time we are able to make awards for the support of the research proposed in only about a third of fully eligible applications.

The extramural programs of the NIH have served well the mission of the agency, and have been a major element in strengthening scientific programs throughout the Nation. There are trade-offs within our basic program instruments however, that under certain conditions can prove to be troublesome. For example, we recognize that a grant for only a single year's support for a research project would in almost all instances be useless and wasteful. Even though the appropriations process does not assure funding for more than a year at a time, we make moral commitments to our grantees for periods of from three to five years. The system is stable and morale is high as long as our annual appropriations permit a reasonable number of new awards each year. But the amount of funding available for new awards is subject to both the level of continuing commitments and to the level of new appropriations. Essentially the amount available for new awards is what's left after continuing commitments are met. In times of constrained budgets a roller coaster effect can develop with regard to new and competing renewal grants, and this in turn can send minor panic through the system. We have not yet developed a means for "buffering" current and prospective grantees from the effects of sudden budget changes.

We have taken steps to remedy some of the problems that have resulted from natural "bureaucratic accretion." In response to the tougher competition and the widespread perception that study sections often look for minor

flaws or omissions in proposals under review and that small factors shift priority scores, applicants tend to over-document. As a result, the workload for both the applicant and the study section is greatly increased.

Although fiscal restraints are responsible for much of the difficulty experienced by the research community, certain attributes of the current extramural award system may be more burdensome than necessary for the investigator, the grantee institution, and the NIH peer review system. In order to increase productivity with the resources available to us, we have instituted several changes in the review and award process.

In our judgement one of the factors that is contributing needlessly to the workload of both the grant applicant and the NIH peer review system is the excessive complexity and the sheer bulk of the research grant application. In addition to page limitations for grant applications, we have taken other steps to reduce the reviewing time for study section members as well as preparation time for the applicant.

We have observed, for example, that when the award rate falls the percentage of successful first-time applicants also falls. It is essential to the vitality of the scientific enterprise and to the morale of the scientific community that young scientists be encouraged. Last year we announced a new program called FIRST awards (First Independent Research Since Training)--a modification that lengthens the awards from three to five years, and the total to \$350,000 of direct costs for the five years. This is intended to obviate the need for too early reapplication for investigators who encounter difficulties in the first 18 months of the term of a grant. It will, we believe, encourage more creative and less defensive research.

Further we have expanded the number and types of longer term support for outstanding mid-career scientists through a program called MERIT awards (Method for Extending Research in Time). This program will involve facilitated extensions of five-year awards for an additional three to five years on the basis of a detailed progress report rather than through reapplication.



Notwithstanding our efforts to fine tune the system, the level of funding continues to be the principal determinant of our ability to nurture the productivity of biomedical research in the United States.

In the absence of funding from federal sources, it too often is necessary for an investigator to defer or even abandon promising research projects. Perhaps more significant in the long run is the effect on the young researcher, who after seven to ten years of post college training has about a one in three chance of gaining independent funding from NIH. We cannot quantify with precision how many decide to consider a change in their career path in the face of such odds, but there are indications that our concerns about this problem are justified.

For example, a recent analysis shows that, on the average, NIH supported investigators are older today than in previous years. The average age of applicants in 1979 was 41.9 years, and in 1985 it was a full year older--42.9 years. There has been a persistent decline in the number of younger applicants for traditional NIH grants. The percentage of all applicants who were under 36 went down from 26.1 percent in 1979 to 13.4 percent in 1986. Stated in number of applications, investigators who were under 36 filed about 3,500 project grant applications in 1979 and a substantially smaller number, about 2,000, in 1986. That was a drop of 41 percent. The decline was even sharper among applicants under 31 where the drop was 79 percent. The significance of these changes is underlined by the fact that investigators 30 and under continue to receive the best priority scores. The second best group is in the band of ages from 31 to 35.

#### New Frontiers in Science

The medical sciences have made great strides throughout the world in the past 40 years. Fields such as genetics, virology, molecular biology, biochemistry and immunology have attracted the brightest and most productive investigators of our era. Discoveries have come so fast that it is almost impossible to keep up with these highly specialized fields. Newly developed instrumentation--taking us from vacuum tubes to transistors, to computer chips; from x-rays to CAT scans to positron emission tomography and magnetic resonance imaging--has permitted amazing leaps in our understanding of

human biology. In particular, scientific attention today is focused on the structural biology of organisms at the cellular and molecular level, and on the mechanisms by which they function properly or fail.

These are more than speculative or theoretical excursions. During this year, for example, the NIH has launched a new program in the structural biology of the AIDS virus, in a special effort to understand this virus at the most minute level of structure possible and to develop new types of drugs against it.

The rapidly increasing sophistication and capacity of computers makes it possible for scientists to give serious consideration to proposals to characterize the entire human complement of genes--the human genome. A decade ago this project would have been considered by many to be a bit of science fiction. But the fact is that the technology for accomplishing it exists today.

There is general enthusiasm for proceeding. We are driven by curiosity, to be sure, but also by the belief that the secrets of the genes will greatly enlighten our quest for new insights about developmental biology, cellular regulation, and disease mechanisms.

Consider, for example, that 4,000 human diseases have a genetic basis, including, for example, cystic fibrosis, Duchenne-type muscular dystrophy, Huntington's disease, and Alzheimer's disease.

The most pressing problem is to devise means for dealing with the vast amount of data that will be generated by the genome project.

Tens of thousands of individual human genes control our life processes. Three and one-half billion units of DNA make up the totality of human genes, or the human genome, and less than half of one percent of them have been sequenced. With current technology, sequencing these billions of units would consume 30,000 person-years and upward of \$5 billion. Fortunately, technology is continuously improved.



Technical advances--including ways to separate large molecules and individual chromosomes--have upped the rate of analysis about ten times in the past decade. A molecular biologist in a technically advanced laboratory today can sequence about 300 DNA units a day. Recent development of an automatic sequencing machine that speeds sequencing tenfold promises to cut the cost for each base in half, from one dollar to fifty cents, perhaps eventually to ten cents.

Databases established to handle DNA sequence information have been swamped. GenBank, which is the principal United States' database, was planned and launched by the NIH's National Institute of General Medical Sciences. It is funded as an interagency project, involving the Departments of Energy and Defense, and the National Science Foundation, as well as four components of the NIH. GenBank is located in the Los Alamos National Laboratory. The European Molecular Biology Laboratory (EMBL) at Heidelberg established a DNA database in 1980. Formal collaborative arrangements were established between GenBank and EMBL in 1982. The challenge is in the extremely rapid growth of the data--from one sequence composed of 76 bases in 1965 to a total of 14 thousand sequences composed of 14 million bases as of October this year. These numbers are expected to increase by twentyfold to fiftyfold in the next five years.

In addition to the problem posed by sheer volume of data is the difficulty created through different data bases using different information systems--different computer languages. Legislation has been introduced to create a National Biotechnical Information Center at the National Library of Medicine on the NIH campus. Experts at such a center would work with the laboratories from which information comes and seek to coordinate data as it is accumulated--to store, process and make it available to the research community nationwide.

If these tasks could be accomplished it would enable scientists to work in a more collaborative style. We feel that such a center is needed to fit together the pieces of the genetic puzzle and acquire the knowledge that would benefit mankind in many ways. With such knowledge we could

develop deeper understanding of the root causes of many disease problems, particularly the ones we know to be inherited.

The possibility of characterizing the human genome has brought us face to face with a question of science policy that could be a forerunner of others we may encounter in the 21st century. The issue is faced more frequently in the realm of physics. It is the question of "little science" versus "big science." More specifically, would an all out effort to carry out the genome project be justified if its pursuit would jeopardize the support of traditional small science investigator-initiated research projects of unknown potential? We seek to find an accommodation that will permit us to pursue the genome without detracting from existing programs.

#### Biotechnology and Research

There need be no better reason for conducting biomedical research than the improvement of human health. This has been central to American policy regarding Government support of such activities. It is a sound base on which to build the policy for the 21st century.

In recent years another justification for government support of research has come into prominence--biomedical research as a foundation for biotechnology. The administration and the Congress have become interested in the economic consequences of our national investment in biomedical research. They see it as a key element responsible for the emergence of biotechnology.

Biotechnology is not a new phenomenon. In fact it has a long history. A century ago, Louis Pasteur was engaged in research that changed, profoundly, the course of the biosciences and medicine. We sometimes forget how industry was also a direct object and beneficiary of Pasteur's work. In lists of his accomplishments we expect to see his pioneering work with vaccines, particularly rabies, and his proof that microorganisms cause fermentation and disease, but we may be startled by the fact that he was equally as well known for having saved the wine, beer and silk industries in France and elsewhere.



Biotechnology has had an impact on the conduct of basic biomedical research comparable perhaps to that of the computer on information processing. Biotechnology has moved us ahead by leaps and bounds in understanding cancer, genetic defects, organ transplantation biology, clinical immunology and allergic response, and bone development and repair, to name a few.

Biotechnology has created an unprecedented set of opportunities, issues and concerns in which the National Institutes of Health has more than a casual interest. This is because the body of knowledge on which the biotechnology industry is based was largely the result of sustained support for basic research in molecular biology and immunology provided by the NIH over the past few decades.

The NIH continues to make a major commitment to the future of biotechnology. The proportion of the NIH budget devoted to biotechnology has remained essentially constant for the past five years, with about 11 percent devoted to directly related research, and about 25 percent devoted to underlying basic research and research training related to biotechnology.

#### Science and Health

A broad description of the role of science in the life of people throughout the world appears in an inscription within the dome of the Great Hall of the National Academy of Sciences in Washington. It reads, "....To Science, Pilot of Industry, Conqueror of Disease, Multiplier of the Harvest, Explorer of the Universe, Revealer of Nature's Law and Eternal Guide to Truth."

Within science and technology the search for new measures for the diagnosis, treatment and especially the prevention of human disease and disability is of preeminent concern, and our national policies concerning biomedical research will continue to be of surpassing importance in the 21st century. Disraeli's wise observation on the subject, however, is timeless, and I will close with it. He stated, "The health of the people is really the foundation upon which all their happiness and all their powers as a state depend."<sup>7</sup>

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<sup>3</sup>U.S. House of Representatives, A Report to the Committee on Science and Astronautics (The Kistiakowsky Report), U.S. Government Printing Office, Washington, D.C., 1965, pp. 84-85.

<sup>4</sup>Keyworth, G.A., III, "Four Years of Reagan Science Policy: Notable Shifts in Priorities," SCIENCE, April 6, 1984.

<sup>5</sup>Executive Office of the President, Special Analyses of the Budget of the United States Government, Fiscal Year 1988, U.S. Government Printing Office, Washington, D.C., p. J 1.

<sup>6</sup>Bush, Vannevar, "Science--The Endless Frontier," U.S. Government Printing Office, Washington, D.C., 1945, p. 18.

<sup>7</sup>Disraeli, The Shorter Bartlett's Familiar Quotations, Doubleday and Co., Garden City, New York, 1952, p. 106.





ANNOTATED AGENDA

55th Meeting of the Advisory Committee  
to the Director, NIH

November 18-19, 1987

Building 31, Conference Room 10  
National Institutes of Health  
Bethesda, Maryland

THE ROLE OF BIOMEDICAL RESEARCH IN COMBATING AIDS

Wednesday, November 18, 1987

MORNING SESSION

8:30 Opening Remarks . . . . . Dr. Wyngaarden

Status of Follow-up Activities to the  
55th Meeting of the Advisory Committee  
to the Director, NIH, "The Health of  
Biomedical Research Institutions"

- Let me extend a warm welcome to the Advisory Committee, Institute Council members, and distinguished guests. This meeting will examine the role of biomedical research in combating AIDS, a topic of high interest and importance to us all. Your views on our efforts to mount a comprehensive and vigorous research

program to understand and treat, and ultimately prevent and cure, this disease are both essential and timely, as now virtually every NIH Institute and Division is participating in this major research initiative.

## NOTES ON COMMITTEE MEMBERS AND COUNCIL ATTENDEES

### Committee Members

- Before turning to our topic, I would like to note that four Committee members were unable to attend:
  - DR. K. FRANK AUSTEN, Chairman of Rheumatology and Immunology, Brigham and Women's Hospital, Boston;
  - DR. JOHN MICHAEL BISHOP, Professor of Microbiology, University of California, San Francisco;
  - DR. ARTHUR GUYTON, Professor and Chairman, Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson; and
  - DR. BERNADINE HEALY, Director, Research Division, Cleveland Clinic Foundation.

Advisory Council Representatives

- Additionally, all Advisory Councils are represented with the exception of the National Advisory Eye Council and the National Advisory Council on Neurological and Communicative Disorders and Stroke. Nine members are representing Councils at this meeting for the first time:
- DR. ROBERT BECKER, Chairman of the Board for HealthCare COMPARE Corporation, headquartered in Downers Grove, Illinois, is representing the National Advisory Environmental Health Sciences Council;
- DR. CHARLES CARPENTER, Physician-in-Chief at the Miriam Hospital in Providence, Rhode Island, is representing the National Advisory Allergy and Infectious Diseases Council;
- DR. KARLA DAMUS, Assistant Professor in the Department of Obstetrics and Gynecology and Director of the Division of Community Health and Epidemiology at the Albert Einstein College of Medicine in the Bronx, New York, is representing the National Center for Nursing Research Advisory Council;
- DR. CALEB FINCH, Professor of Gerontology and Biological Science at the University of Southern California, Andrus Gerontology Research Center in Los Angeles is representing the National Advisory Council on Aging;



- DR. DANIEL FOSTER, Professor of Internal Medicine at the University of Texas Health Sciences Center in Dallas is representing the National Diabetes and Digestive and Kidney Diseases Advisory Council;
- DR. FRED JONES, Dean of the School of Graduate Studies at Meharry Medical College in Nashville is representing the National Advisory Dental Research Council;
- DR. WILLIAM KOOPMAN, Director of the Division of Clinical Immunobiology and Rheumatology at the University of Alabama in Birmingham is representing the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council;
- DR. JOHN MURRAY, Professor of Medicine at San Francisco General Hospital is representing the National Heart, Lung, and Blood Advisory Council; and
- DR. DAVID SATCHER, Director of Meharry Medical College in Nashville, Tennessee, is representing the National Advisory Research Resources Council.

STATUS OF FOLLOW-UP ACTIVITIES TO THE  
55TH MEETING OF THE ADVISORY COMMITTEE TO THE DIRECTOR, NIH  
"THE HEALTH OF BIOMEDICAL RESEARCH INSTITUTIONS"

- As a result of our last meeting in June where we addressed the topic of "The Health of Biomedical Research Institutions," a number of activities have been initiated. As you know, this meeting served to initiate discussion of the general characteristics and specific elements of the current Federal system of sponsored research that are contributing to stability of biomedical research institutions and influencing the quality, creativity, and scientific productivity of the biomedical research enterprise.
- There appeared to be general agreement that the academic research system is not in imminent danger of collapse although there is growing evidence--much of it anecdotal--that many serious problems that had long been chronic are now taking on a greater sense of urgency.
- It was clear from these discussions that the university environment has changed profoundly over the past several decades and continues to change, at least in part, in response to the expanded role that universities have assumed in meeting the national research and research training needs.

- There was also a general view expressed that a growing discrepancy exists between the facts concerning the policies, programs, and funding of the NIH and the perceptions that have gained currency in the scientific community regarding such factors.
  
- Accordingly, it was agreed that it would be useful to extend and intensify the deliberations of the June meeting through a series of regional meetings to be conducted under the auspices of this Committee on "The Health of Biomedical Research Institutions." It was decided that the purpose of the meetings would be two-fold:
  - First, to describe the broad political context in which the NIH operates, to dispel some of the popular myths concerning NIH budgets and programs, to discuss the broad goals and strategies that condition and influence current and emerging NIH policies and practices, and to encourage members of the scientific community to develop and maintain a keen awareness of the process by which science budgets are developed and to increase their active participation in that process; and
  
  - Second, to solicit through public testimony the views of biomedical researchers, university faculty and administrators, representatives of professional societies, and other interested parties concerning the issues affecting the health of biomedical research institutions.



- As you know, this series of meetings is now under way. And I appreciate the effort that the members of this Advisory Committee have shown in contributing their time and energies to this activity.
- The first two meetings were held on November 5 in Los Angeles and November 6 in San Francisco.
- I believe we received an enthusiastic response from members of the academic community in those areas and the NIH looks forward to the future meetings. The next ones are in New York on December 3 and Boston on December 4.
- We will be prepared to present a full report on the results of all these meetings at our June 1988 meeting.

8:40 Responding to a Public Health Emergency:  
The Scope and Dimensions of Biomedical  
Research Directed at the AIDS Problem . . . Dr. Wyngaarden

## INTRODUCTION

- The clinical manifestations resulting from infection by the Human Immunodeficiency Virus, particularly in its most pernicious form, Acquired Immunodeficiency Syndrome is one of the most formidable challenges currently facing the biomedical research community.

This challenge extends beyond scientific boundaries and into the areas of research management, science policy, and public policy.

- The Advisory Committee to the Director, National Institutes of Health, has always been an important source of advice and counsel on difficult research and science policy issues. This meeting can serve as an effective stage from which we can review our AIDS research activities in a comprehensive fashion and examine the direction, composition, and management of our efforts.
- Therefore, the purpose of this 2-day meeting is to examine how government, academia, and industry have responded to the AIDS epidemic in terms of the SCOPE and DIMENSIONS of its effort, and how major aspects of the effort are ORGANIZED and MANAGED. As part of this overall review we also will address FUTURE SCIENTIFIC DIRECTIONS in AIDS research.
- AIDS has reminded many of us that the public's perception of the role of biomedical research is not always consistent with those who manage and conduct research. Accordingly, I want to stress that while the principle focus of this meeting will be on our combined efforts to understand, treat, and prevent this disease at the biological level, we also must be responsive to the broader context within which biomedical research is conducted.

- It is my hope that this meeting will enhance our understanding and appreciation of the many interrelationships between those social, political, ethical, and economic issues that can influence the conduct of AIDS biomedical research.
- As we move through the agenda, it is my expectation that this meeting will present a clear picture of the role of biomedical research in altering the course of this epidemic and how we work in a collective and constructive manner, both within and outside the research community, in combating this disease.
- Given the priority associated with AIDS research, I have taken steps to establish a special Advisory Committee to the Director, formally called the AIDS Program Advisory Committee. Later, I will tell you more about the composition of this group and how it fits into our overall management and planning of AIDS research.
- Although the AIDS Program Advisory Committee is not yet operational, I anticipate that our deliberations today will accelerate their work by serving as a point of departure in identifying components of the AIDS problem requiring continuing analysis and discussion.



## SCOPE AND DIMENSIONS

- Nearly 7 years have passed since the initial reports of a unique disorder, that was eventually identified as AIDS, reached the Centers for Disease Control. During that period of time, the NIH AIDS research budget has grown rapidly and has expanded in a number of different directions.
- As a first step in our discussions, I would like to present some data that characterizes the scope and dimensions of AIDS research in terms of NIH support and how these resources are allocated across mechanisms and organizations here at NIH.
- The first slide (SLIDE 1) simply shows the overall growth of NIH AIDS funding from FY 1982 through the President's proposed budget for FY 1988. The most distinctive feature of this budget is a rapid rate of growth at a time when there is considerable overall restraint in the Federal budget.
- (SLIDE 2) The next level of analysis of this budget involves the use of selected "Functional Categories" that are commonly used for PHS budget and planning purposes. These functional categories are:
  - Pathogenesis and Clinical Manifestations
  - Therapeutics

- Vaccine Development and Evaluation
  - Public Health Control Measures
  - Patient Care and Health Care Needs
  - Multidisciplinary AIDS Research
- The majority of activities undertaken by NIH fall within the first three categories. Public Health Control Measures and Patient Care and Health Care Needs are largely within the purview of other components of the Public Health Service. The "Public Health Control Measures" category, however, includes the prevention of transfusion-related AIDS and the development of blood tests which is a major responsibility of the National Heart, Lung, and Blood Institute.
  - Multidisciplinary AIDS research includes those activities that form a broad base of support for research spanning a number of disciplines.
  - (SLIDE 3) The next slide shows how the AIDS budget has been apportioned under these categories. As you can see, while most of our activity was initially in the area of understanding the pathogenesis and clinical manifestations of this disease, that began to change significantly starting in FY 1985 when support for the development of therapeutics was sharply increased.

- This data graphically reflects the basic philosophy behind our current approach, namely, that we are attempting to develop effective interventions and control measures while at the same time intensifying our investigations in the nature of the etiologic agent, conducting and expanding epidemiologic and natural history studies, strengthening research in immunology, and attempting to develop appropriate animal models. All of these approaches fall in the Pathogenesis and Clinical Manifestations category.
- The next slide (SLIDE 4) examines how NIH resources are apportioned across extramural and intramural lines. Over time, you can see that the relationship of intramural to extramural funding is approaching a distribution characteristic with overall NIH support.
- You will also note a special "OD" category. Normally, the Office of the Director does not provide direct support for research programs; however, Congress has provided special discretionary funding within the Office of the Director for AIDS. Currently, these funds are being used to support a special program of "structural biology" that applies modern techniques of molecular structure determination and analysis in the development of antiviral drugs in the treatment of AIDS. Approximately one-half of the funding in this program is within the intramural research program and the other half is in the form of program project grants.



- (SLIDE 5) The next slide details how the extramural component of AIDS funding is apportioned across various funding mechanisms. This graph demonstrates that a large portion of our extramural support has been in the area of contracts. Given the rapid evolution of the AIDS problem, the contract mechanism proved to be the most effective mechanism at that time to quickly expand our efforts. Given the fact that we now have in place many of the major components of the AIDS program, I believe that we must shift more of these resources into the area of individual research grants, and I have already initiated actions to accomplish this shift. ["Other" category includes: other research grants--3 percent, training--less than 1 percent, research management support--2 percent.]
- This pie chart (SLIDE 6) demonstrates that while the NIAID and NCI play the key role in overall NIH effort, approximately 25 percent of our budget is distributed among other components of NIH, principally NHLBI and DRR. The next slide (SLIDE 7) examines the "other" category in more detail and shows relative range of involvement of the other Bureaus, Institutes, and Divisions.
- I feel this type of deployment is a sound approach in that it places the primary emphasis for our effort within the two organizations having the greatest relevance to this problem while also supporting research across all the other components of NIH.

The broad level of involvement allows us to draw upon the unique strengths and capabilities that are embodied in the various components of NIH. For example, the National Institute of Neurological and Communicative Disorders and Stroke plays a strong role in examining the neurologic aspects of HIV infection including the problems associated with delivering therapeutics across the blood brain barrier. The National Institute of Child Health and Human Development pays particular attention to the issues of AIDS involving mothers, children, and reproductive biology. (Slides Off/Lights On)

## ORGANIZATION AND MANAGEMENT

- The implications for such a large and complex set of research activities is that it must be accompanied by a particularly strong and well-defined management structure. This need is heightened by the intense level of concern that has surrounded AIDS and the need to accelerate research in this area.
- Since the earlier days of the AIDS epidemic NIH has had in place a coordinating committee, however, in October 1985, I took action to strengthen NIH's capacity to coordinate and plan AIDS research by naming Dr. Fauci as the NIH AIDS Coordinator and reconstituting the NIH AIDS Executive Committee.
- The membership of this Committee is limited to Institute Directors and principal OD staff with a designated alternate who has the authority to speak for the Institute Director. Later

this morning Dr. Fauci will provide additional details on the composition and responsibilities of this group when he and Dr. Windom address some of the actions that have been taken both at the agency level and the overall PHS to coordinate AIDS research and related activities. Also, we will hear a report from Dr. Bick describing some of our efforts to accelerate the extramural awards system in the support of AIDS research.

- In addition, we are honored to have with us today, Senator Kennedy, who will tell us about the Senate's efforts to impart a greater sense of direction and structure to all components of the Federal AIDS effort.
- I believe the National Institutes of Health has and should continue to serve as the leader in stimulating AIDS biomedical research, identifying and supplying special research resources, attracting and training new scientific talent, and bringing together representatives of the research community to discuss the problems and opportunities facing this national effort.
- In the area of coordination, I believe we need to carefully examine arguments calling for significant change in our current management approach. In my view, there are many aspects of biomedical research that argue for a considerable degree of flexibility; since excessive centralized control can sometimes result in a bureaucratic process that retards creativity and slows the ability of biomedical research to change directions.



- Striking the appropriate balance between too much or too little coordination is a difficult task, and I hope you will share your individual perspectives on this issue.
- As part of our effort to improve the management of AIDS research, we need to take into account the material and human resources necessary to keep pace with the intense level of reporting and accounting associated with AIDS research. While we readily recognize our responsibility to keep the public and the press informed, at times the burden of a myriad of requests for information can retard and place stress on the actual performance of the research.
- It should be recognized that reporting on AIDS research often involves exercising scientific judgment and that there are a limited number of skilled scientific staff capable of developing meaningful reports. Any plans for improving coordination and management should take into account the resources necessary to provide for adequate research reporting.

#### FUTURE DIRECTIONS

- To those who maintain that the scientific establishment has not moved quickly enough in conducting research on AIDS, it should be pointed out that, in a very real sense, the biomedical research community initiated AIDS research over 20 years ago. Prior

support of basic science established a foundation of fundamental knowledge in those areas directly related to HIV and AIDS, areas such as cellular immunology, virology, microbial genetics, and molecular biology. In addition to our knowledge base, we also have developed entirely new technologies that are essential in our efforts to develop efficacious vaccines and therapeutics.

- Without this prior investment it would have taken decades to have achieved what has been accomplished during the past 5 years. This clearly supports an approach in which applied research must be balanced with a vigorous basic research program.
- I believe it is worth underscoring the fact that, had AIDS emerged in the preceding decade(s), we would have been at a severe disadvantage in our attempts to understand this disease.
- Fortunately, we have made impressive strides in understanding the nature of this disease, and later in the program, we will be hearing presentations from a number of leading researchers who will bring us up to date on advances in the areas of pathogenesis, treatment, vaccine development, and the molecular biology of HIV.
- In addition to the substance of the science, there is a related issue that deserves consideration during this meeting. Has the biomedical research community done enough to convey to the public

the sense of commitment, resolve, and vigor that characterizes our response to the AIDS problem?

- Have we conveyed to the public a sense of the numerous scientific challenges and opportunities that lay before us in approaching the AIDS problem? We no longer rely solely on serendipity to provide answers, rather we are moving our efforts forward in a deliberate and direct fashion.
- As part of the discussion on the future directions for AIDS research, we need to address our existing and future research capacity. For example, are we doing enough to strengthen our needs in the area of human resources? Should we be doing more in evaluating the capacity and training within those disciplines that have the greatest relevance to AIDS research?
- Finally, I think we should also give some thought to the broad implications that this disease has for the future of biomedical research. While the challenge of AIDS is immense, our efforts in this area may well enhance our understanding of many other disease processes.
- More importantly, the resolution of the AIDS epidemic offers biomedical research an opportunity to make yet another enduring contribution to mankind. The eventual conquest of AIDS should forever validate the wisdom of those early visionaries, who



decades ago recognized the value of furthering our understanding of medicine and biology.

#### INTRODUCTION FOR SENATOR KENNEDY

- We are fortunate to have with us today, the Honorable Edward M. Kennedy, Senator from the State of Massachusetts. As most of you know, Senator Kennedy has been formulating a major piece of legislation entitled, the Acquired Immunodeficiency Syndrome Research and Information Act of 1987.
- We have asked Senator Kennedy to share his perspectives on our national AIDS research effort and the activities of the U.S. Senate to strengthen and enhance our research capacity.

9:00 U.S. Senate - Proposals and Actions  
to Strengthen the Nation's Capacity to  
Combat AIDS . . . . . Senator Kennedy

9:30 Discussion

9:40 The Administrative Structure  
Established to Coordinate the  
Federal Research Effort  
Against AIDS

Chairman . . . . . Dr. Wyngaarden

- In this next segment of the program we will concentrate on the various administrative steps that have been taken to strengthen the coordination of AIDS research both at the agency level and at the level of the Public Health Service.

- Dr. Fauci will begin the discussion--

- Initiatives Undertaken by NIH  
to Strengthen Coordination  
Within the Agency and With the  
Health Research Community. . . . . Dr. Fauci
- Initiatives Undertaken by the  
PHS to Coordinate the National  
AIDS Program . . . . . Dr. Windom

10:20 Coffee Break

10:30 Discussion

10:45 Establishing Priorities for AIDS  
Research Support. . . . . . Dr. Wyngaarden

- Taken in its entirety the process by which we establish priorities for AIDS research represents an extremely complex series of actions taking place both within and outside of Government, and within settings as diverse as molecular biology laboratory and the halls of Congress.

- Now that Drs. Fauci and Windom have provided us with a perspective on the coordination of AIDS research, both within agencies and at the level of the Public Health Service, we should be in a better position to discuss the overall processes by which we determine the future course and direction of our AIDS research effort.
- One of the most important elements of priority setting at NIH involves the interaction that takes place between Federal science managers and their non-Federal counterparts in the form of advisory councils, committees, boards, and panels. This takes place at multiple levels and includes both ongoing and short-term advisory bodies.
- As Dr. Fauci pointed out earlier, some of the Institutes have strengthened their normal advisory council structure by establishing subgroups to deal specifically with those aspects of AIDS research relevant to their organizations.
- This has also occurred in the Office of the Director. During the summer and fall of 1986 a special group of ad hoc consultants were assembled for a series of four meetings in which they examined AIDS research issues and requirements and developed a report on the future directions for AIDS research. Dr. Charles Carpenter, who is here today as the Advisory Council representative for the National Institute of Allergy and Infectious Diseases, served as the overall chairman of this group.



- This group of consultants were divided into three panels, one examining pathogenesis and natural history, another on vaccine and prevention activities, and the third on treatment, opportunistic infections, antivirals and immune reconstitution. Dr. Bernard Fields chaired the pathogenesis group, Dr. Couch chaired the vaccine group, and Dr. Hirsch chaired the treatment group.
- Their report, "Future Directions for AIDS Research," is one of the documents included in your briefing material. I believe this document serves as an excellent example of the way in which we can integrate the advice of the extramural community in helping to identify AIDS research priorities.
- While we were gratified that the report supported our actions at that time, it also indicated, within each of the three major categories, where future emphasis was needed.
- For example, in the area of pathogenesis and natural history, they suggested that in the future greater effort be placed in
  - Furthering our understanding of basic immunologic mechanisms and of the early pathogenic events associated with HIV infection and clarification of the sequence of events by which infection is established.
  - Definitive studies of the neurologic aspects of HIV infection.

- Continuing and extending studies of the natural history of HIV infection, the immunopathogenesis of AIDS, and the generation of better epidemiological data for estimating the prevalence of HIV infection in high- and low-risk groups in various areas of the United States and other geographic locations where there are distinctive patterns of HIV infection.
- In the area of treatment and antivirals, it was recommended that we place greater emphasis on the
  - Development and implementation of new clinical protocols to evaluate AZT and other antivirals in a wide variety of HIV-associated conditions and the strengthening of drug discovery programs and animal model studies to identify, develop, and evaluate new antiviral agents that act by a variety of mechanisms to inhibit HIV replication.
  - Expansion of efforts to develop and evaluate new treatments for opportunistic infections and neoplasms in pediatric as well as adult AIDS patients.
- In the area of vaccine development, their report suggested that we extend our efforts in the

- Development of animal models suitable for elucidating the pathogenesis of HIV and for evaluating candidate vaccines and the development of recombinant DNA methods for production of each viral protein and selected peptides and the characterization of the function of these proteins in the infectious process.
- Evaluation of various vaccine candidates and approaches in suitable animal models, including surface glycoprotein vaccines, whole virus vaccines, peptide vaccines, recombinant viral vector vaccines, anti-idiotypic vaccines, and suitable live attenuated vaccines.
- Much of the growth of ongoing AIDS research activities that has taken place since these "areas for future emphasis" were developed has evolved along the pathways identified in this report.
- I believe the approach that was used in developing this report was sound and needs to be continued.
- One of the major administrative recommendations of their report was to make the process of reviewing the NIH AIDS research effort an ongoing one, and that such an ongoing review would strengthen the ties between NIH and the extramural community. Accordingly, I initiated actions to establish a formally chartered AIDS Program Advisory Committee.



- The charter for this Committee was signed by Secretary Bowen in September and since that time we have been striving to bring the appropriate members on board and initiate the work of this group.
- The purpose of this Committee will be to advise the Secretary; the Assistant for Health; the Director, National Institutes of Health; the NIH AIDS Coordinator; and the NIH AIDS Executive Committee on long- and short-term planning to meet research needs in AIDS. Specifically, this Committee review of the overall NIH AIDS research effort is designed to ensure that the NIH AIDS research effort is both internally consistent and complimentary with efforts taking place in non-Federal research settings, and that NIH efforts are directed at those scientific opportunities which offer the greatest potential. The Committee would also provide advice on policy questions and other matters concerning the NIH AIDS research program.
- This Committee will be composed of 13 members--nine scientists knowledgeable in the areas of molecular biology, immunology, virology, neurology, pediatrics, vaccine development, antiviral development, clinical care, animal model research, retrovirology, structural biology and epidemiology and four public members.

- It is interesting to note that the release of the report of the Ad Hoc Consultants coincided closely with the release of the National Academy of Sciences, Institute of Medicine report, "Confronting AIDS." Although the IOM report went beyond the area of research within the context of biomedical science, I believe the two separate reports were harmonious and reinforced the need to extend our efforts along the prescribed lines.
- "Confronting AIDS" was also extensively utilized at NIH in analyzing and establishing AIDS research priorities. Shortly after the IOM report was released, NIH initiated an exhaustive analysis of the 79 recommendations contained in the report dealing with future research needs. The results of this analysis, a document of over 100 pages in length, was compiled and was used as a tool in comparing both our current and future research activities with those emphasized in the IOM report itself.
- In a few minutes we will be hearing more about the upcoming activities of the IOM.

#### Planning Process

- Another element involved in the process of establishing AIDS research priorities is the annual planning sessions. These sessions are designed to identify and provide a forum for the

review of scientific initiatives offering the greatest opportunity to advance our understanding of human disease.

- These sessions involve a series of meetings between myself, the senior officials within the Office of the Director, each of the Institute Directors and their senior staff.
- Normally each session is devoted to the activities of one Bureau, Institute, or Division; however, given the priority that we have placed on AIDS, I have instituted a separate planning session devoted exclusively to AIDS. The session is orchestrated by Dr. Fauci in his role as the NIH AIDS Coordinator.
- This year the AIDS planning session will cover a range of research opportunities, some of which will include future plans in the areas of AIDS targeted antivirals, AIDS vaccine development, animal models for HIV infection, clinical trials of HIV immune globulin, pulmonary and cardiac complications in HIV infection, seroepidemiologic surveys, investigations into the pathogenesis of neuro-AIDS and associated HIV related neurological disorders.
- Given the fact that representatives from all of the Bureaus, Institutes, and Divisions involved in AIDS research attend this session, it allows for an exchange of views on future AIDS research initiatives. Further, it provides me with a better



appreciation of where each of the Institutes will be placing emphasis in the coming years.

- While most of the topics discussed at these sessions involves the actual conduct of science, the discussions also touch upon issues having to do with the underlying structure within which research is conducted. For example, we will also address issues such as AIDS research facilities, biocontainment animal research space, instruments to study viral structure and function, and for computer modeling.
- As we move through the various stages of formulating future AIDS research priorities, we eventually reach a stage where we begin to build these initiatives into next year's budget. As I'm sure you are all aware, the budget development process is a highly structured decision making process involving the agencies, the Public Health Service, the Department of Health and Human Services, the Office of Management and Budget, congressional appropriations committees, and the prevailing economic climate.
- Once again, given the urgency associated with AIDS, the development of the AIDS budget operates on an independent track and is coordinated at NIH through the NIH AIDS Executive Committee and at the level of the PHS through the PHS AIDS Task Force.

- Finally, we come to the most compelling factor that ultimately sets our future research agenda, that is the state-of-knowledge of the disease. Establishing AIDS research priorities is inherently dependent upon the unfolding scientific realities of AIDS and will continue to play the leading role in shaping the scope of our future efforts.

11:00 Status of Activities of the  
National Academy of Sciences  
Institute of Medicine  
AIDS Oversight Committee. . . . . . Dr. Widdus

11:30 The Role of Basic Undifferentiated  
Research in the Conquest of AIDS  
and Perspectives on AIDS Research  
Management. . . . . . Dr. Baltimore

12:00 Discussion

12:15 Lunch

#### AFTERNOON SESSION

Chairman . . . . . Dr. Wyngaarden

- As we begin this afternoon's session, we will examine closely the efforts that have been undertaken to expedite the award of AIDS

extramural research projects. Dr. Katherine Bick, Deputy Director for Extramural Research, will now provide us with a overview of these efforts.

1:30 Efforts to Expedite the AIDS

Extramural Awards . . . . . Dr. Bick

2:00 Discussion

2:15 Advances and Next Steps in Understanding  
the Structure, Function and  
Replication of HIV

Speakers . . . . . Dr. Wong-Staal

2:45 Discussion

3:00 Coffee Break

3:15 Advances and Next Steps in Understanding  
the Pathogenesis and Natural History  
of AIDS

Chairman . . . . . Dr. Fields

Speakers . . . . . Dr. Johnson  
Dr. Fauci

4:15 Discussion

4:30 Adjourn



Thursday, November 19, 1987

MORNING SESSION

Chairman . . . . . Dr. Fauci

8:30 Advances and Next Steps in the Treatment  
of AIDS

Chairman . . . . . Dr. Hirsch

Speakers . . . . . Dr. Broder  
Dr. Volberding

9:30 Discussion

9:45 Coffee Break

10:00 Advances and Next Steps in AIDS Vaccine  
Development

Chairman . . . . . Dr. Couch

Speakers . . . . . Dr. Fischinger

10:40 The Role of Chimpanzees in  
Vaccine Development . . . . . Dr. Hilleman

11:00 Discussion

11:15 The Public's Attitudes and Concerns  
Regarding the Federal AIDS Research  
Effort. . . . . . Dr. Osborn

11:45 Discussion

12:00 Lunch

## AFTERNOON SESSION

1:00 Collaboration With the Private Sector

Chairman . . . . . Dr. Chabner

Speakers . . . . . Dr. Barry

1:40 Research Results to Patients/IntellectualProperty. . . . . . Dr. Harmison

## 1:50 Discussion

## 2:00 Coffee Break

2:15 Status of Resources Necessary to Underpin  
the National AIDS Research Effort (Facilities,  
Animal Models, Research Investigators)

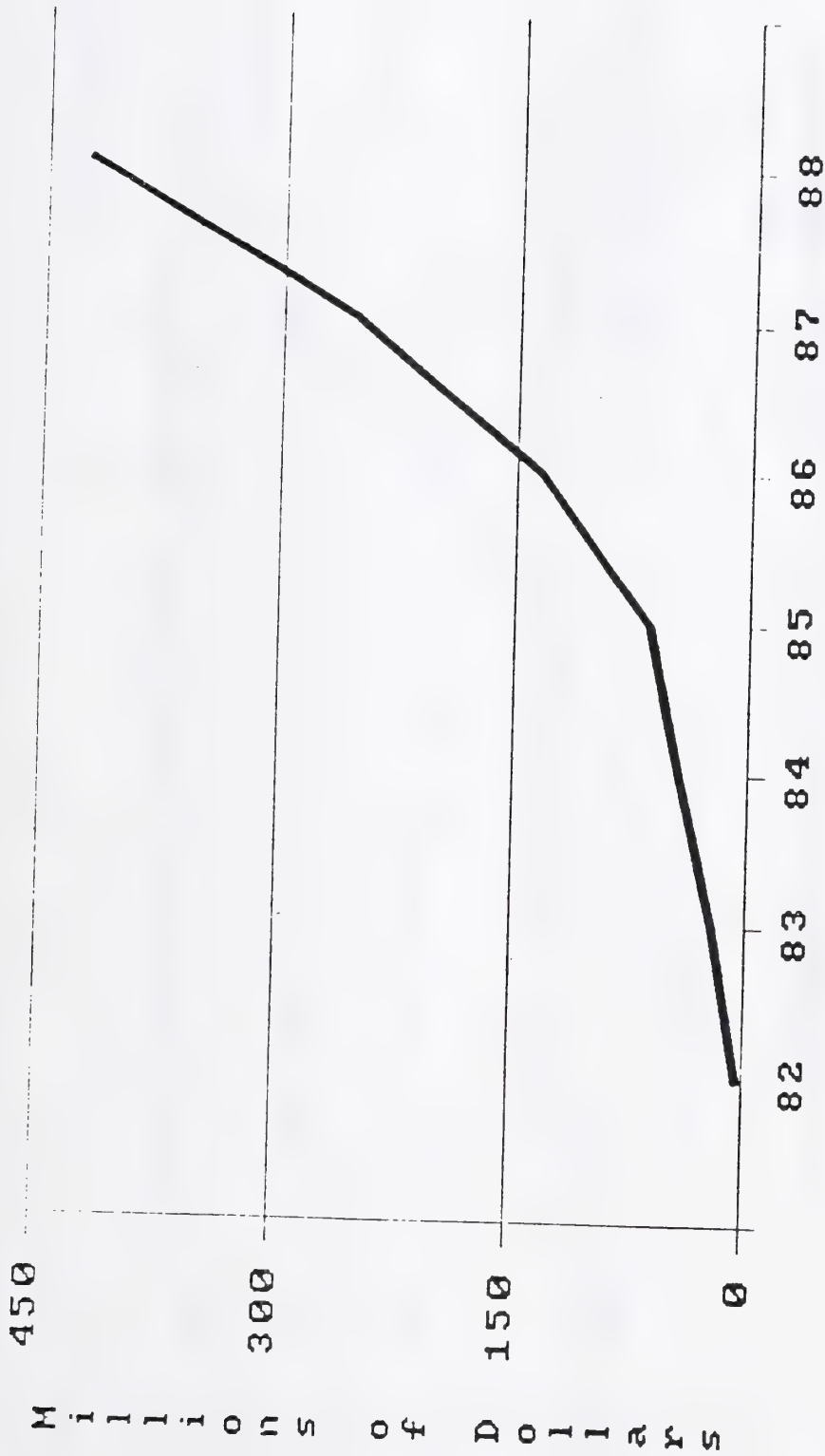
Speaker. . . . . Dr. Wolff

## 2:45 Discussion

## 3:00 Concluding Remarks. . . . . Dr. Wyngaarden

## 3:15 Adjournment

**Total AIDS Funding**  
**Fiscal Years 1982-88**



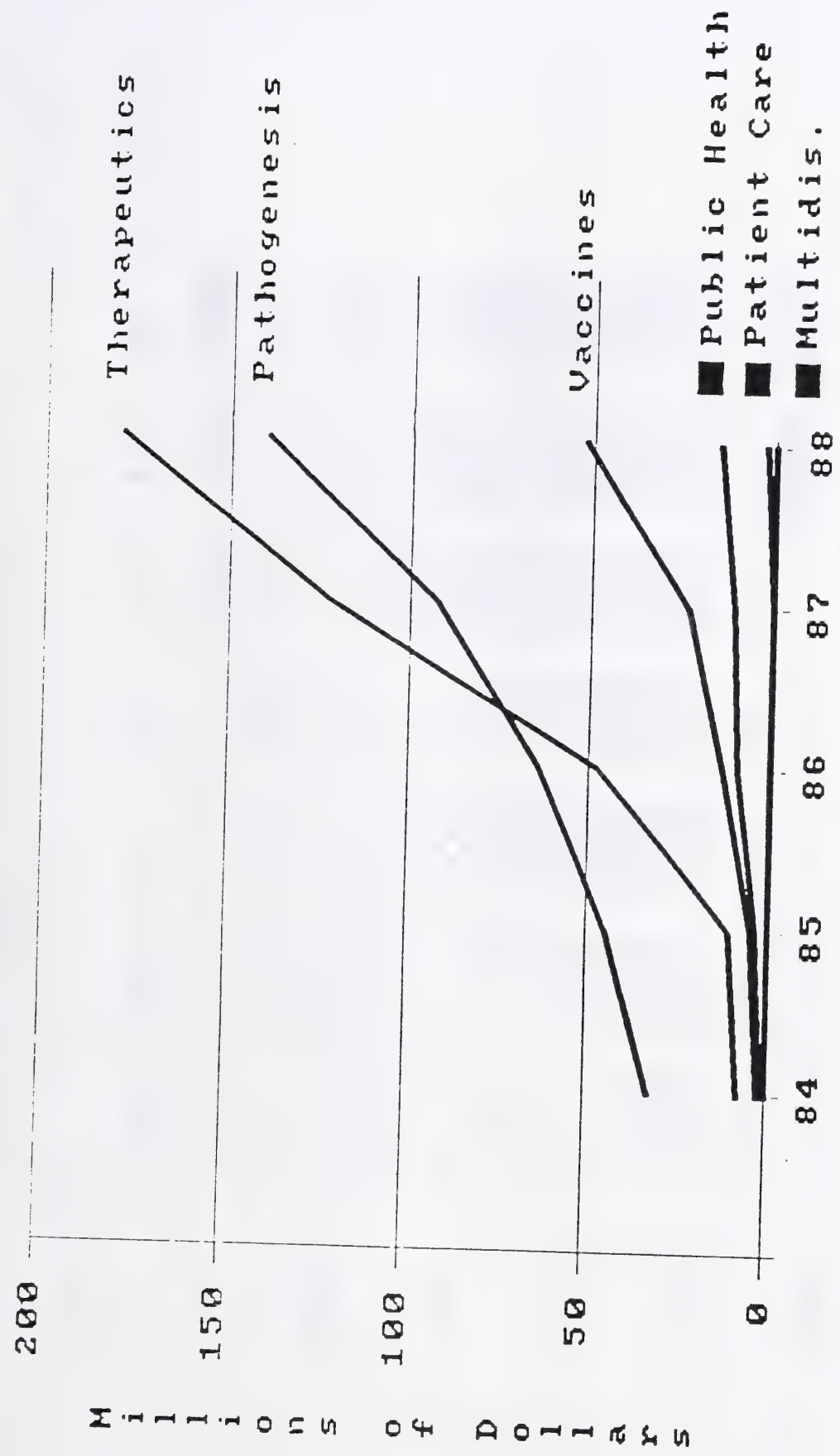
OPPE October 1987



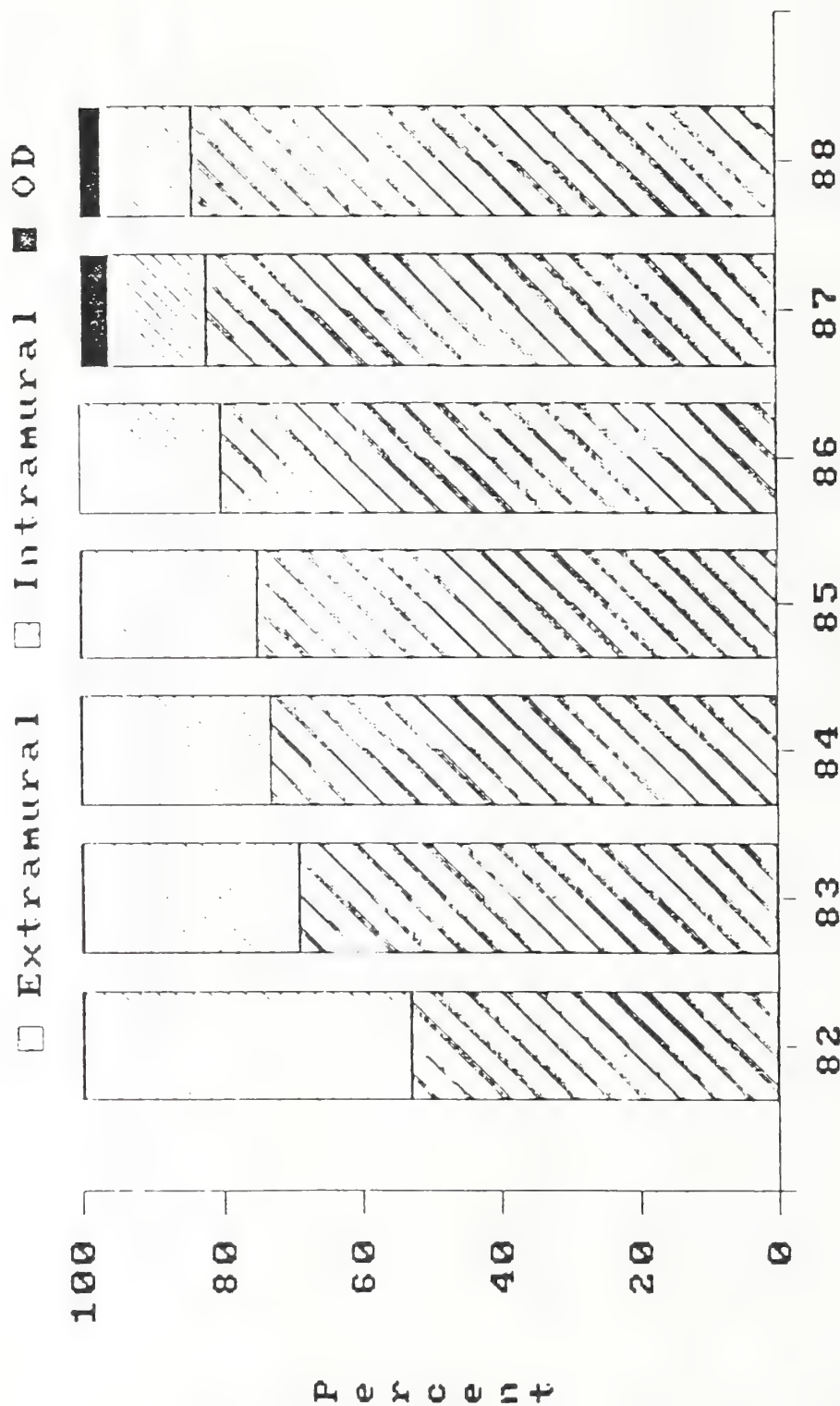
# NIH AIDS Functional Categories

- o Pathogenesis & Clinical Manifestations
- o Therapeutics
- o Vaccine Development & Evaluation
- o Public Health Control Measures
- o Patient Care & Health Care Needs
- o Multidisciplinary AIDS Research

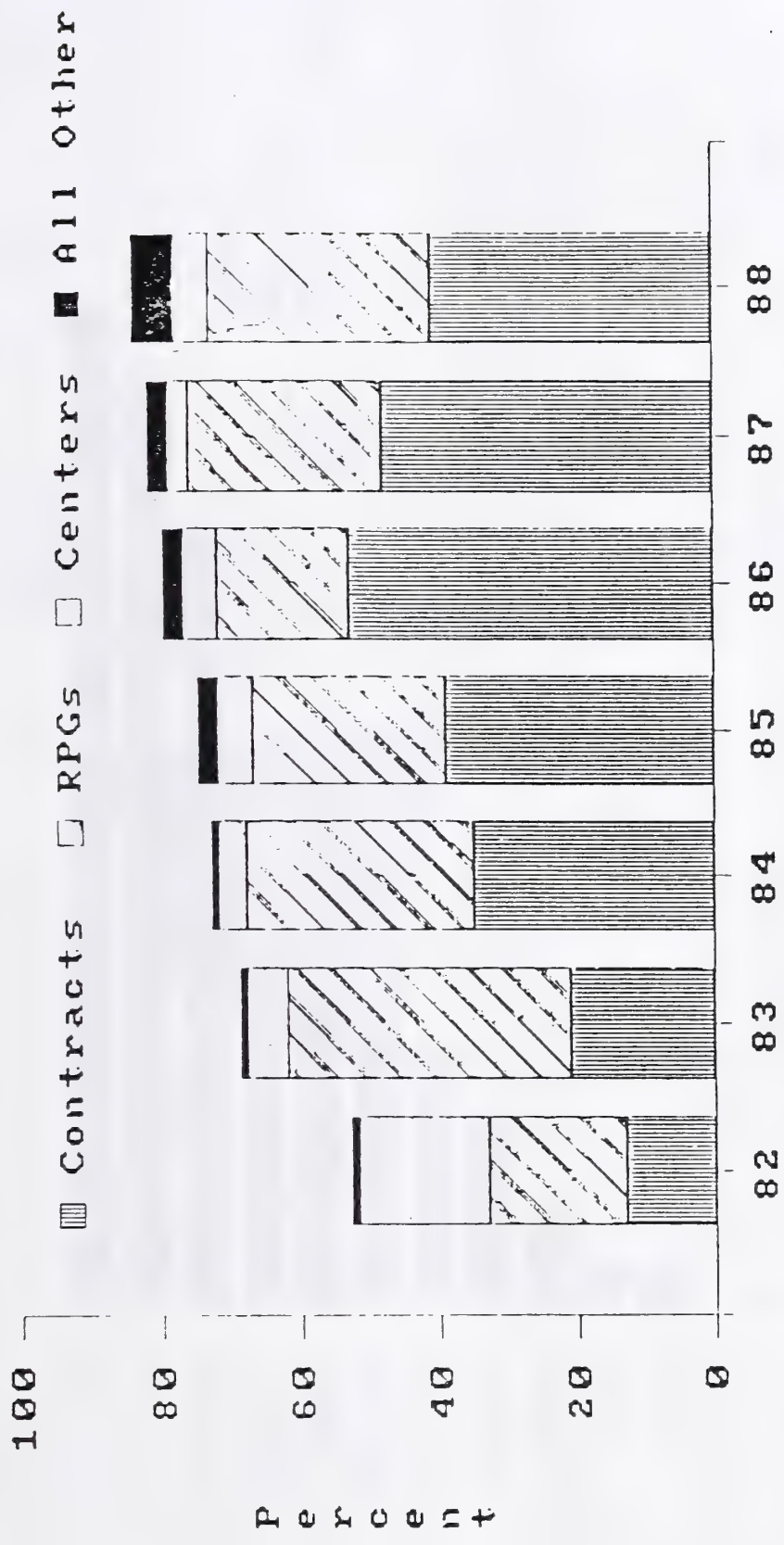
# **MH AIDS Funding** **by Multidisciplinary** **Fiscal Years 1984-88**



# Percentages of AIDS Funding by mechanism Fiscal Years 1982-88

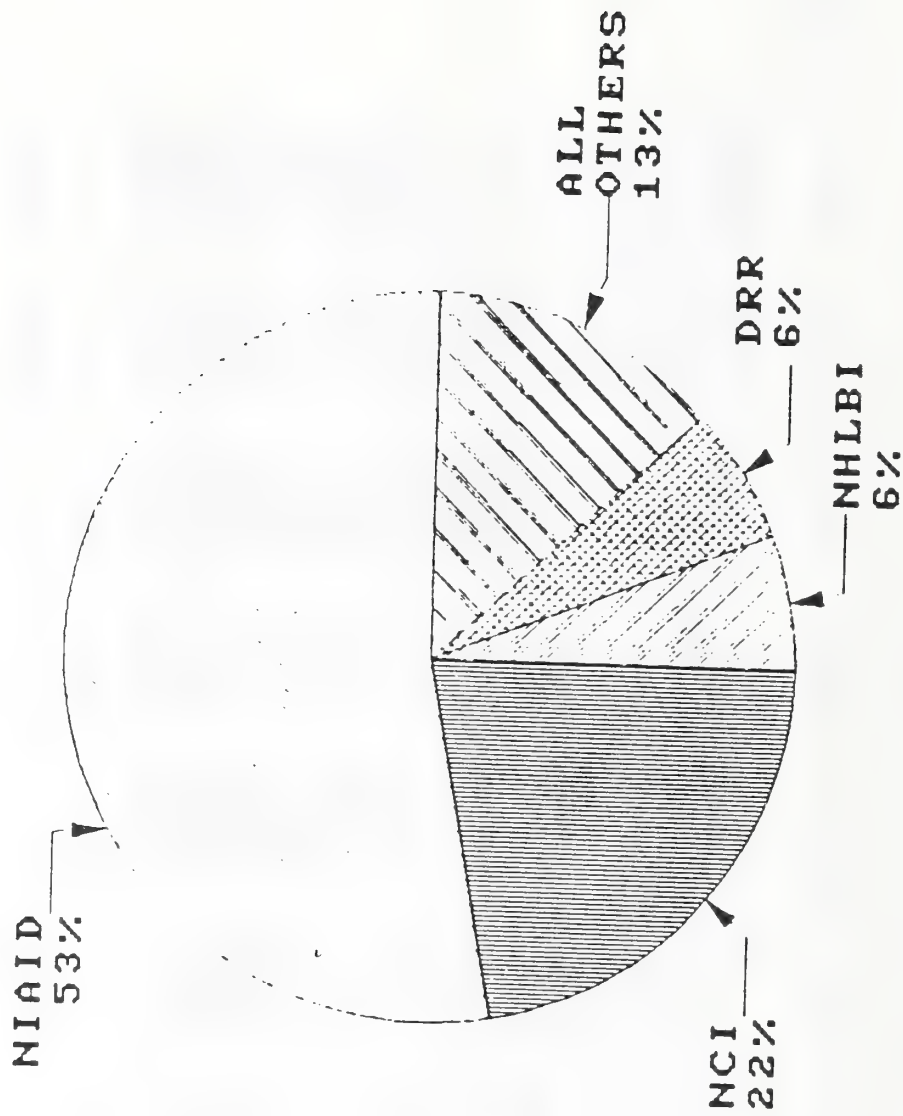


# Distribution of External AIDS Funding Fiscal Years 1982-88





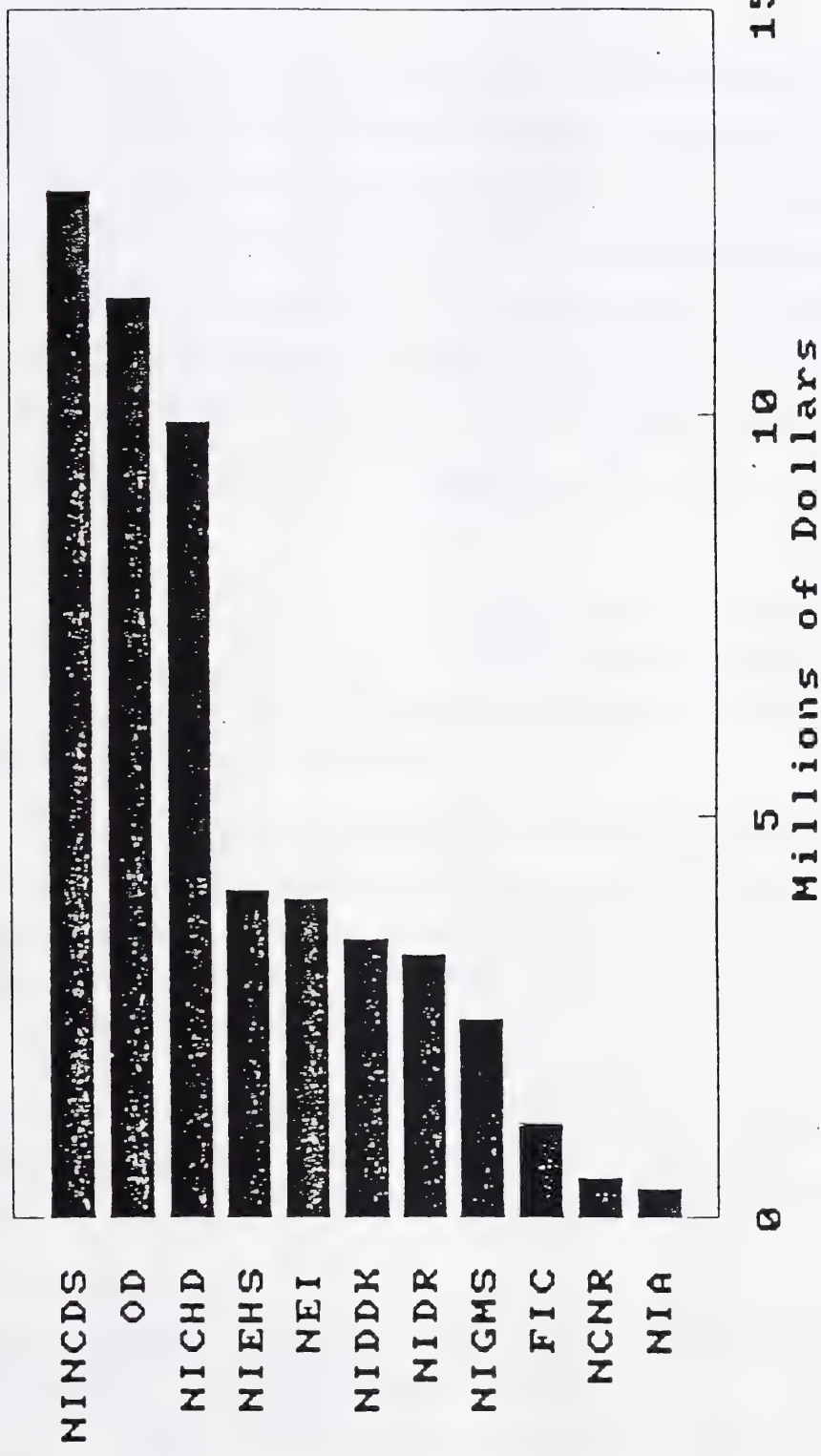
# AIDS Funding by BID FY 1988 Amended President's Budget



Source: DFM/NIH

OPPE October 1987

# AIDS Research Funding for Selected B/I/Ds \* in Amended President's 1988 Budget



Source: DFM/NIH  
 \* B/I/Ds with AIDS Research less than \$25 million  
 OPPE October 1987



MORTIMER LIPSETT--THE BID DIRECTOR\*

by

James B. Wyngaarden, M.D.\*\*

In the ceremony that is to follow, a few of Mort Lipsett's friends and colleagues will speak for his friends everywhere in appreciation of different facets of the life and work of this unusual man. I am to talk of him as an Institute Director but it will not be possible for any of us to stick strictly to an appraisal of any one aspect of his accomplishments, nor would it be appropriate to do so. For Mort's strength was through the application of his wide range of abilities to the challenges and opportunities at hand. Each of the presentations will reinforce an appraisal common to all who know him, that his qualities as a leading scientist and as an interested, caring person were key elements in his success as a scientist-administrator.

There are few, if any, positions in government, science, or in academia that match the challenges and opportunities presented by the post of an Institute Director. Fewer still are the individuals who can meet those responsibilities as well as Mort did.

Mort brought to his directorship of the Clinical Center, and two of our Institutes, a brand of enthusiasm that propagated itself rapidly throughout the organization he headed. His was the kind of self-assurance that translated readily into leadership, because it clearly came from successful experience.

And much of that experience was gained at the NIH, so that he had an extremely valuable store of knowledge about the people, policies and practices of the NIH. This resource he put to good use wisely and

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\*Remarks presented at the dedication of the ACRF Auditorium, National Institutes of Health, in memory of Dr. Mortimer B. Lipsett, November 20, 1987.

\*\*Director, National Institutes of Health, Bethesda, Maryland





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\*\*Director, National Institutes of Health, Bethesda, Maryland

decisively, so that in short order it was clear to all that he was an unusually effective leader and administrator.

But from his prior experience he gained something more valuable than bureaucratic facility. It gave him a broad perspective, and with that perspective an appreciation "in the round" of the agency as a whole.

His nonparochial view of the NIH was understood and valued by his colleagues, particularly his fellow Bureau/Institute/Division Directors. Inevitably he became a respected advisor and leader among them. When he spoke at the regular BID meetings or the "brown bag" sessions, he was heard and heeded. And I hardly need to add that his advice was respected and valued in Building One.

He had the instinct for timing that is characteristic of gifted leaders in science and the administration of science. It enabled him to sense when the time was opportune for the application of nascent insights to the solution of long-standing and stubborn problems. He could foresee, better than most, the coming together of a need and the means of meeting it, and thus he was able to bring about unusual accomplishment. He knew when the time was ripe--when a research effort or a program had reached a decision point, and then he had the wit and courage to make the necessary decisions.

Another quality, essential to an effective NIH Institute Director, is an understanding of the public nature of this institution, a realization of the keen public concern for the successful outcome of our efforts against disease and disability. There appears to be an almost insatiable public hunger for information about health matters and legitimate interest in the process as well as the progress of research. The ability to inform and even teach the public's representatives in the Congress is a special responsibility of an Institute Director, and Mort was an able advocate before congressional committees. But his avid interest in communicating information on the importance of science, biomedical research and medicine was not confined to presentations at committee hearings.

It was Mort who originated and carefully launched the "Medicine for the Layman" series of lectures. In the 11 years since the series began, more than 30,000 persons have attended the lectures, and overflow audiences are the norm. The tapes made from the lectures continue to be in demand through booking agents and on cable television, and the audience is numbered in the millions. The remarkable success of this program is owed in large measure to his insistence on high quality of every aspect that went into the planning and development in the early years, a tradition that has been maintained. A mention of this program that Mort carried out imaginatively and successfully is especially appropriate to this occasion. It is representative of his special interest in communication as a vital part of the scientific enterprise--not only communication with research investigators and clinicians, but also with the public at large. Communication with all of these audiences is the function and purpose of the facility we dedicate today to the memory of our friend. I believe he would be pleased to know that we will call it the Mortimer B. Lipsett Auditorium.





REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

It has been my good fortune to serve as Director of the National Institutes of Health during the year in which the centennial of its founding has been observed. Although I had expected observances at our headquarters in Bethesda, and some at other locations, I was not prepared for the number of centennial events that have been held in the United States and throughout the world; nor did I anticipate the warmth with which our many friends have joined with us in marking this occasion just as you have done in such an outstanding way.

Permit me, personally and officially on behalf of the National Institutes of Health, to express profound gratitude to our Belgian colleagues for bringing together this company of some of the leading scientists of our day in honor of the hundredth birthday of the NIH.

The early history of the NIH is closely identified with European science of the late 19th century. The 1880s and the 1890s were years in which a rapid expansion of knowledge was taking place that opened up new areas of human endeavor. It was a time of solid scientific advances, particularly in the fields of chemistry, physics and biology.

Medical science in the United States lagged far behind the state of knowledge in Europe. Studies in the new discipline, bacteriology--led by Koch, Pasteur and Lister--were being carried out in increasing numbers of European laboratories, but few Americans were participating, either at home or abroad.

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\*Presented at the National Fund for Scientific Research ceremony celebrating the NIH Centennial, Brussels, Belgium, December 2, 1987.

\*\*Director, National Institutes of Health, Bethesda, Maryland

In the early 1880s the United States was in the grip of fear that the cholera pandemic of 1881 might be imported from overseas. This concern prompted health authorities to send a young American doctor, Joseph Kinyoun, to study with Koch, who had discovered the cholera bacillus in 1883. It was hoped that insights that Dr. Kinyoun would gain in the Koch and Pasteur laboratories would suggest means for preventing a wave of cholera in the United States.

Upon his return Dr. Kinyoun advocated the establishment of a bacteriological laboratory in the European mold. In 1887 he set up the modest Laboratory of Hygiene at the Marine Hospital on Staten Island, New York. The National Institutes of Health is the lineal descendant of that Laboratory.

The first steps toward realization of Dr. Kinyoun's goal to make the laboratory a national resource were taken four years later when the small facility was moved to temporary quarters in Washington. By 1904 it was settled in newly constructed buildings in downtown Washington where it remained for 35 years. During this period and until the end of World War II the NIH operated as a small, freestanding Government laboratory--the research arm of the Public Health Service. Most of the efforts of the agency were devoted to solving such riddles as the cause of infectious diseases and then providing the knowledge for their prevention.

In 1930 the United States Congress passed legislation to broaden the scope of the mission of the agency to include responsibility for "....ascertaining the cause, prevention and cure of disease." It was then that the Congress gave the name "The National Institute of Health" to the Laboratory.

The modern era of the NIH, as well as of biomedical research in the United States, began when the Government and non-Government research laboratories, mostly in academic institutions, joined their efforts in carrying out biomedical research in World War II. To meet the urgent need for additional knowledge on how to deal with the health problems of the personnel in the military services, the U.S. Government turned to

established non-Federal academic and independent laboratories to conduct vital research. Grants and contracts were awarded for the support of such essential investigations. The arrangement resulted in acceleration of progress in research and development across the entire spectrum of health related problems.

By the end of the war the U.S. Office of Scientific Research and Development was administering a large number of medically related research projects--some 250 were being conducted at universities, medical schools, hospitals and pharmaceutical companies. When the OSRD was disbanded the health research projects were assigned to the National Institute of Health. The decision not only confirmed the agency's role as the principal biomedical research arm of the Federal Government, it also established Government support of research in non-Government institutions--the NIH extramural programs--as the dominant mechanism for carrying out biomedical research in the United States.

Increases in the NIH budget have been spectacular since the extramural programs were established. The total appropriation of the agency grew at an average rate of 24 percent per year for more than 20 years from 1945 to 1968. Although there was an inevitable tapering off of the rate of growth, the increases have continued almost without interruption, even in the periods when the Federal budget for controllable domestic programs has been constrained. Since 1967 the NIH budget has gained about 2 percent per year, but in the past five years the NIH support has increased by about 6 percent per year.

The rapid expansion of support and of the organization to carry out the expanded programs has mirrored public concern about specific diseases and general categories of health problems. The names of the 12 institutes constitute a kind of historical catalog of American worries and hopes about health. It is not surprising that the first to be established were the National Cancer Institute and the National Heart Institute.

Even though many of the Institutes were given disease-specific missions, our commitment to basic research has been sustained and is now a substantial



component in the research programs of each of the institutes. In the early 1970s, the fraction of the total NIH budget devoted to basic research was no more than 45 percent. By 1980 this portion had reached 52 percent, and in 1986 it was 63 percent.

By its nature the celebration of an anniversary suggests appraisals of the past and of the future. One of our final centennial activities will be to assemble materials to be placed in a time capsule that shortly will be sealed, not to be reopened until the year 2087. Certain of our senior personnel have been asked to prepare statements addressed to our successors three or four generations hence. In these statements program officials are asked to describe two or three important discoveries made recently in their respective organizational entities.

The project set me to thinking how I would summarize the principal accomplishments of the NIH in the course of its first century.

Perhaps the most significant contribution of the National Institutes of Health is the pioneering work in molecular genetics that began in the 1950s and continues unabated. This research has led to a virtual revolution extending across all of the biological sciences. It is the foundation for the recombinant DNA technique whose possibilities are only beginning to be realized. An entirely new biotechnology industry is based on discoveries in molecular biology.

I would be pleased for our successors to be reminded that the NIH was deeply involved in molecular genetics when this discipline first emerged, and that we had a part in bringing it into the mainstream of science.

Among the accomplishments of the first century I would also count among the most important the establishment of the organizational mechanisms by which we carry out our mission. We call them our intramural and extramural programs.

Slightly more than one-tenth of the NIH budget is devoted to the conduct of research in NIH's own laboratories. About 2,500 doctoral level

scientists and 3,500 trained support staff are engaged in our diversified intramural research program at the forefront of biomedical research. The intramural program has had a powerful impact on American science directly through the significant contributions to the knowledge base that have emerged from the NIH laboratories. It has also exerted a lasting influence upon American science through its training programs. We offer a variety of structured experiences for postdoctoral trainees in the clinical and basic sciences. At this time almost 900 young scientists are participating in our regular training programs. After leaving the NIH these scientists have become leaders in academia and industry, and have had a profound influence on science in the United States.

In addition to our regular training programs we conduct the NIH visiting programs for talented scientists from throughout the world, who come to Bethesda to share with us their expertise as they work together with our scientists in the NIH laboratories. Currently 1500 scientists from other countries are participating in research at the NIH (of whom 15 are from Belgium).

The other organizational accomplishment, that I believe to be fully as important, was the establishment of our extramural programs, by which we are able to draw upon the creativity and the expertise of essentially the total American biomedical research community.

The system was built on the basic tenet that it should protect the integrity and independence of the research worker and the researcher's freedom from control, direction, regimentation and outside interference. Under that program, which has been in operation for 40 years and is allocated between 80 and 90 percent of the NIH budget, scientists throughout the Nation submit applications for research projects they propose to conduct. The projects to be funded are selected in open competition, and in the selection process we rely heavily upon the appraisals by non-Federal scientific peers of the applicants. In this manner the system engages the expertise of scientists throughout the Nation, both in the conception and the conduct of the research, as well as in the evaluation of research proposals. Currently more than 50,000

scientists are engaged in conducting research supported by the NIH at some 1600 institutions in the United States and in other countries.

I have talked in specifics about some of the steps that have been taken by the NIH in the course of the century whose completion we are observing. But in closing, I will turn to an eloquent and sweeping appraisal of the advances of the whole of science by one of the distinguished participants in today's excellent program, Professor Christian de Duve. He wrote a superlative assessment of the recent progress of science that I have quoted a number of times at centennial observances. "Although it is always difficult to judge one's own time in historical perspective," he said, "one cannot help the feeling that the second half of this century will be remembered for one of the great breakthroughs of human knowledge--perhaps the greatest to date, as it concerns the basic mechanisms of life."<sup>1</sup>

#### REFERENCE

- <sup>1</sup>De Duve, Christian, A Guided Tour of the Living Cell, Scientific American Books, Inc., 1984, p. 17.

# PRESENT OVERVIEW OF THE NIH--INTRA- AND EXTRAMURAL FUNDING\*

by

James B. Wyngaarden, M.D.\*\*

Personally and on behalf of my associates at the National Institutes of Health I wish to state our profound gratitude to our good friends who have planned this special occasion to mark the centennial anniversary of the National Institutes of Health. The theme of international cooperation in biomedical research stated in the introduction to today's proceedings is exemplified in many of the presentations that we have heard. In these ceremonies, and at the substantial number of Centennial symposia held in different parts of the world, I have been inspired and delighted to learn how scientists and scientific programs have been mutually supportive and productive across continents, oceans and international borders.

When we began to plan how the Centennial of the National Institutes of Health might appropriately be observed, we did not anticipate the number of ceremonies, seminars, conferences and other events that would be held in the United States and throughout the world. Neither did we anticipate the warmth with which friends such as you would join us in celebrating our anniversary.

Representatives of the NIH have been honored guests at splendid anniversary celebrations in five continents. Without detracting in any way from what has been done in other parts of the world, I must acknowledge the special way in which the NIH has been honored in Europe. The ties between our agency and our colleagues in Europe have always been close.

The early history of the NIH is closely identified with European science of the late 19th century. The 1880s and the 1890s were years in which a rapid expansion of knowledge was taking place that opened up new

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\*Address presented at the Work Day on Health and Biomedical Research, Ministry of Health and Consumption, Madrid, Spain, December 9, 1987.

\*\*Director, National Institutes of Health, Bethesda, Maryland



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Medical science in the United States lagged far behind the state of knowledge in Europe. Studies in the new discipline, bacteriology--led by Koch, Pasteur and Lister--were being carried out in increasing numbers of European laboratories, but few Americans were participating, either at home or abroad.

In the early 1880s the United States was in the grip of fear that the cholera pandemic of 1881 might be imported from overseas. This concern prompted health authorities to send a young American doctor, Joseph Kinyoun, to study with Koch, who had discovered the cholera bacillus in 1883. It was hoped that insights that Dr. Kinyoun would gain in the Koch and Pasteur laboratories would suggest means for preventing a wave of cholera in the United States.

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The rapid expansion of support and of the organization to carry out the expanded programs has mirrored public concern about specific diseases and general categories of health problems. The names of the 12 Institutes constitute a kind of historical catalog of American worries and hopes about health. It is not surprising that the first to be established after the original NIH, which in effect was an infectious diseases institute, were the National Cancer Institute and the National Heart Institute.

Even though many of the Institutes were given disease-specific missions, our commitment to basic research has been a substantial component in the research programs of each of the institutes. In the early 1970s, the fraction of the total NIH budget devoted to basic research was no more than 45 percent. By 1980 this portion had reached 52 percent, and in 1986 it was 63 percent.

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Perhaps the most significant contribution of the National Institutes of Health is the pioneering work in molecular genetics that began in the 1950s and continues unabated. The research at this frontier conducted and supported by the NIH has led to a virtual revolution extending across all of the biological sciences. I was delighted to learn that Dr. Severo Ochoa would participate in today's ceremony, for he played a uniquely important role in the pioneering studies of that period. He was one of the first to provide evidence as to how the energy from metabolism is stored and utilized. In 1955 he described the finding of an enzyme system that led to the

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synthesis of compounds resembling naturally occurring ribonucleic acid (RNA). It was for this work that he was awarded a share of the 1959 Nobel Prize with Arthur Kornberg. The NIH is greatly honored to have contributed through its grant programs some of the support that enabled such leaders in science to carry out their immensely important studies.

I would be pleased for our successors to be reminded that the NIH was deeply involved in molecular biology when this discipline first emerged, and that we had a part in bringing it into the mainstream of science.

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In addition to our regular training programs we conduct the NIH visiting programs for talented scientists from throughout the world, who come to Bethesda to share with us their expertise as they work together with our scientists in the NIH laboratories. Currently 1500 scientists from other countries are participating in research at the NIH (of whom 36 are from Spain).



The other organizational accomplishment that I believe to be fully as important was the establishment of our extramural programs, by which we are able to draw upon the creativity and the expertise of essentially the total American biomedical research community.

The system was built on the basic tenet that it should protect the integrity and independence of the research worker and the researcher's freedom from control, direction, regimentation and outside interference. Under that program, which has been in operation for 40 years and is allocated between 80 and 90 percent of the NIH budget, scientists throughout the Nation and indeed throughout the world may submit applications for research projects they propose to conduct. The projects to be funded are selected in open competition, and in the selection process we rely heavily upon the appraisals by non-Federal scientific peers of the applicants. In this manner the system engages the expertise of scientists throughout the nation, both in the conception and the conduct of the research, as well as in the evaluation of research proposals. Currently more than 50,000 scientists are engaged in conducting research supported by the NIH at some 1600 institutions in the United States and in other countries.

There need be no justification for national support of biomedical research than the improvement of human health. This has been central to American policy regarding government support of such activities. It is a sound base upon which to build our policies for the future.

In recent years another justification for government support of research has come into prominence--biomedical research as a foundation for biotechnology. The administration and the Congress have become interested in the direct economic consequences of our national investment in biomedical research. They see it as the key element responsible for the emergence of biotechnology.

Biotechnology, in turn, has had an impact on the conduct of basic biomedical research comparable perhaps to that of the computer on information processing. Biotechnology has moved science ahead by leaps and bounds in understanding cancer, genetic defects, organ transplantation biology,

clinical immunology and allergic response, and bone development and repair, to name a few.

The NIH continues to make a major commitment to the future of biotechnology. The proportion of the NIH budget devoted to this subject has remained essentially constant for the past five years, with about 11 percent devoted to directly related research, and another 25 percent devoted to underlying basic research and research training related to biotechnology.

A broad description of the role of science in the life of people throughout the world appears in an inscription within the dome of the Great Hall of the National Academy of Sciences in Washington. It reads, "....To Science, Pilot of Industry, Conqueror of Disease, Multiplier of the Harvest, Explorer of the Universe, Revealer of Nature's Law and Eternal Guide to Truth."

Within science and technology the search for new measures for the diagnosis, treatment, and especially the prevention of human disease and disability is of preeminent concern, and a nation's policies concerning biomedical research will continue to be of surpassing importance in the 21st century. Disraeli's wise observation on the subject, however, is timeless, and I will close with it. He stated, "The health of the people is really the foundation upon which all their happiness and all their powers as a state depend."<sup>1</sup>

#### REFERENCE

- <sup>1</sup>Disraeli, The Shorter Bartlett's Familiar Quotations, Doubleday and Company, Garden City, New York, 1952, p. 106.



ADDRESS\*

by

James B. Wyngaarden, M.D.\*\*

We are at that point in the budget cycle when the financial offices of Federal agencies are in a frenzy of preparation for the annual appropriations hearings. The Office of Management and Budget has given us the details of the President's budget request for Fiscal Year 1989 and we are putting together our presentations in support of it. This is taking place within less than a month of the time when Congress completed action on appropriations for Fiscal 1988. It is almost a Grand Convergence of the budgets, and while not a celestial event it is indeed a time of intense and accelerated meditation.

Some of the events that preceded the convergence provide an example of the issues that can arise in government funding of research. The 1988 appropriation for the National Institutes of Health was a part of a massive continuing resolution signed by the President on December 22. But Fiscal Year 1988 began October 1, so we were uncertain for virtually the first quarter of the current fiscal year as to what funds would be available for the ongoing programs of the NIH. The uncertainty was accentuated because it was not known until the last moment whether the automatic reductions feature of the Gramm-Rudman legislation would be levied against whatever appropriation might be passed.

This double uncertainty caused us to restrict our grant awards during the interim period to those that would be made under the most stringent fiscal conditions. Under normal circumstances we award a substantial number of grants each year on December 1. While we were confident that funds would be available for most of our grant commitments we did not feel it

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\*Address presented at the second "Medicine for the 21st Century" forum at the Rancho Mirage, Palm Springs, California, January 20, 1988.

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appropriate to make full awards to the December grants when doing so might make it necessary to make serious cuts in grants to be awarded later in the year.

For those who may not be fully familiar with NIH programs I should note that our average grant is made for a period of from three to four years. Federal funding, however, is on an annual appropriations basis, so that each year we make noncompeting renewal grants for support of those projects to which we have a continuing commitment. Grants that have run their full term may be renewed but only in competition. Thus we have an important category of competing renewal grants each year.

After careful consideration of the problem, we decided that prudent management required us to confine our December 1 awards essentially to non-competing renewal grants, and to limit them to a funding commitment of three months at the FY 1987 level. The number of competing renewal grants was sharply curtailed. The plan provided for a very few new grants--only the ones that clearly were of highest priority.

Such steps are not lightly taken because we know their impact upon the confidence and morale of the affected investigators and on the grantee institutions where the research takes place. We took special pains to keep all concerned fully informed about our actions and our plans. From the reports I have received it appears that essentially all members of the grantee community understood the necessity for our action, and did not panic even though for many of them any major reduction in grant funding could have brought on serious problems. Happily, in early January we were able to advise all awardees that 12 months funding at the approved level would be provided for the grants that had been made at reduced levels. And we are now in a position to make new awards.

The recently approved FY 1988 appropriation for all activities of the National Institutes of Health is \$6.67 billion. Included in this total is almost \$450 million for research on AIDS, as compared with about \$250 million for AIDS in Fiscal Year 1987. Because of the major increase allocated to this one large program area, a more representative appraisal of the NIH budget increase can be made by comparing the non-AIDS portions

of the appropriations for the two years. Viewed in this way the increase in the NIH budget from 1987 to 1988 was 4.8 percent. If AIDS funding is included the increase from one year to the next amounts to 7.8 percent. However, these apparent increases are somewhat illusory, for a closer examination of the budget reveals that the non-AIDS increase for the National Cancer Institute was 2.8 percent and for the National Heart, Lung, and Blood Institute 3 percent, in neither instance keeping up with rising costs.

Notwithstanding these reservations, it is encouraging to note that the past six years have seen sustained growth of the total appropriation of the NIH, amounting to 83.2 percent in current dollars and 30.4 percent in real terms. This growth has erased the 14 percent loss in purchasing power experienced by the NIH from FY 1979 through FY 1982. In each of these last six years the NIH appropriation has reached a new high in constant dollar terms.

The congressional action making the 1988 appropriation specified the number of research grants to be made during the year at a total of 6,052 new and competing renewal research project grants. The funding available for these grants was also specified, and thus in effect the legislation fixed the average cost per grant. We estimate that with the funds available it will be necessary for us to "negotiate downward" the funding for individual continuing research project grants by 7 percent, and for competing projects by 10 percent below study section recommended levels. These necessary reductions vary from Institute to Institute so that the range extends from 4 percent to 12 percent. This practice forces grantee institutions to accept a degree of cost-sharing over which they have no control from year to year and raises a question of public policy. While the congressional action is not an overt requirement for cost-sharing, it results from the compartmentalization of the NIH appropriations, where line items delineate the amounts to be expended for grants and for other support mechanisms, with the further constraints that arise from the non-transferable character of overall appropriations to individual institutes.

For the first two decades subsequent to World War II the budget of the NIH grew at the spectacular rate of 24 percent per year. But owing largely

to the stresses of the Vietnam war, the NIH budget took a step backward so that the appropriation for 1968 was below that of the previous year. The mark that had been reached in 1967 was not exceeded until 1970. Some leaders in the scientific and academic communities saw this brief recession as the beginning of the end of Federal support for biomedical research, yet since that time the NIH appropriation has increased more than fourfold.

But the NIH of 1988 is not an enlarged copy of the NIH of 1970. The times are different and our internal and external challenges are not the same. There has been considerable discussion in the press recently about the the so-called "privatization" of the NIH. Without engaging in a discussion of the sketchy proposal, I will repeat what I have told a number of reporters--that the proposal is an indication that at the highest levels of government some of the NIH problems, particularly with salary levels and related micromanagement, have been recognized.

We have been fortunate indeed to have been able to recruit and retain the calibre of scientists now conducting the large intramural research programs of the NIH. The highest salary we are able to pay under the Federal pay cap, about \$ 84,000 per year, is just about half the average salary being paid to clinical department chairmen in American medical schools. Time and time again we have seen scientists, whom we are recruiting for important positions, turn away because of the surprisingly low salary, even though they obviously had sincere interest in the position being offered. We have lost to academia and industry some of our fine leaders who had no desire to leave the NIH but because of personal financial responsibilities were forced to move.

It is very hard to imagine how a major restructuring of the NIH, such as "privatization," could be done without jeopardizing the excellent quality of the uniquely balanced and effective organization; but perhaps there are less drastic measures that could lead to the solution of some of our severe problems.

Since 1970 there have also been a number of qualitative changes in the patterns of program funding. For example, in the early 1970s the fraction of the total NIH budget devoted to basic research was only about 45 percent.

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This figure had reached 52 percent, and in 1986 it had grown to 63 percent. This trend is further reflected in the prominent position that investigator-initiated research project grants have grown to occupy at NIH. In 1970 NIH funded 10,000 such awards, in 1982 the number was 15,970, and the newly approved budget will fund 19,800 such awards. More than 56 percent of the total NIH budget for 1988 will be devoted to the support of the traditional project grants. In 1970 project grants were assigned a little over 41 percent of the total budget.

This increase in the number of research project grants has been a result both of slow, steady budget growth and of a reduced emphasis upon contracts, and to some extent on centers. There has also been a decline in the fraction of the budget devoted to training that resulted primarily from the elimination of non-research training following the 1974 revision of authorizing legislation. The increased percentage of the budget devoted to project grants reflects these shifts of funds among support mechanisms.

I have put primary emphasis on supporting individual investigators, because of my belief that the most important things in biological science come out of "small science." Fortunately we can both meet our commitments and emphasize basic science when the budget is increasing. So, in recent years as we have prepared our budgets we have stressed the defense of the investigator-initiated research project grant.

One important element in the grant budget has remained essentially the same over the past 15 years--that is the average total cost of research project grants expressed in constant dollars. For instance, the average total cost of grants in 1986 was about the same as the average cost in 1972 when both are expressed in constant dollars.

The total costs of grants have two major components. One is the direct costs--the amounts required for the services of the investigators and support staff--and the costs of necessary supplies and items specifically required by the research project. The other category--indirect costs--accounts for the expenses to the grantee institution resulting from the research project.



Even though the total amount of the average grant has remained about constant for several years, there has been a reduction in the portion available to the investigator. The reason is that since 1972 the indirect cost component for all grant awards has increased from 21 percent to 31.4 percent of the total award, and accordingly, in constant dollar terms the average direct cost of research project grants has declined 13 percent in the past 15 years.

The increases in indirect cost have occurred in roughly three phases. At first, such costs were strongly influenced by the rising costs of energy--lights, heat and related costs. When those increases began to taper off, another factor began to have influence--the administrative costs to the grantee institutions resulting in part from additional Federal accounting and institutional review requirements. These costs have essentially stabilized, so that now the component on the increase reflects a changing institutional pattern of funding, so that the "use costs" of money and depreciation of facilities are the chief factors driving indirect costs upward.

In year to year comparisons of appropriations and of research grants, I have referred frequently to constant dollars. Perhaps I should be more specific about our definition of constant dollars. The Federal Government routinely publishes many different price indexes, for example, the Consumer Price Index (CPI). Specialized indexes are frequently constructed for particular organizations or agencies.

The Biomedical Research and Development Price Index (BRDPI) is a specialized price index estimated by the Bureau of Economic Analysis of the Department of Commerce specifically for the National Institutes of Health. It is designed to reflect movements in the prices paid by NIH for the conduct and administration of biomedical research and development services, and it more accurately adjusts the annual nominal budget for changes in prices than does a more general price index, such as the CPI or the implicit price deflator for the Gross National Product (IGD).

The percentage change in the BRDPI exceeded the percent change in the IGD in each of the seven years from 1980 to 1986. It also exceeded the CPI

during the last five of those seven years. Thus, if the more general indexes had been used instead of the specialized BRDPI, the inflation in biomedical prices would have been underestimated and the real purchasing power of the NIH budget would have been overestimated. The BRDPI places a much higher weight on expenses of universities and medical schools than the more general indexes.

Not only has the pattern of funding programs of the NIH changed during the past 20 years, there has been a marked change in the national pattern of support of medical research. In 1967 the NIH was the source of 47 percent of all of the funds devoted to medical research and development in the United States. At that time industry funded 25 percent and private non-profit foundations and organizations had dropped to 8 percent. Estimates for 1987 show industry as the source of 41 percent, the NIH of 34 percent, and private non-profits at 4 percent.

From the beginning the preeminent and fully sufficient justification for the expenditure of Federal funds in support of biomedical research has been the essential role it plays in the improvement of human health. Another purpose for Federal support of biomedical research has recently come on the scene--biomedical research as the foundation for biotechnology. The Administration and the Congress have become interested in the economic consequences of our national investment in biomedical research. They recognize it as the key element responsible for the emergence of biotechnology.

Biotechnology, in turn, has had an impact on the conduct of basic biomedical research, comparable perhaps to that of the computer on information processing. Biotechnology has moved us ahead by leaps and bounds in understanding cancer, genetic defects, organ transplantation biology, clinical immunology, allergic response and bone development, to name a few.

Biotechnology has created an unprecedented set of opportunities, issues, and concerns in which the National Institutes of Health has more than a casual interest. This is because the body of knowledge on which the biotechnology industry is based was largely a result of sustained support

for basic research in molecular biology and immunology provided by the NIH over the past few decades. The NIH continues to make a major commitment to the future of biotechnology.

The rapidly increasing sophistication of laboratory techniques and the expanded capacity of computers makes it realistic for scientists to give serious consideration to proposals to characterize the entire human complement of genes--the human genome. There is general confidence that discovery of secrets of the genes will greatly enlighten our quest for new insights about developmental biology, cellular regulation, and disease mechanisms.

The possibility of characterizing the human genome has brought us face to face with a question of science policy that has been encountered in other disciplines more frequently than in the biosciences. It is the question of "little science" versus "big science." Would an all-out effort to carry out this project be justified if its pursuit would jeopardize the support of traditional basic science investigator-initiated research projects of unknown potential? We seek to find an accommodation that will permit us to pursue the genome without detracting from existing programs.

In closing I wish to say a word in general about the funding of biomedical research by the Federal Government. In recent years it has not been uncommon for university officials, presidents of professional societies, heads of voluntary agencies, and others to proclaim that the National Institutes of Health appropriations have been slashed, that the Federal support of biomedical research is capricious, and the future uncertain. Based on the facts and from my firsthand experience, I am impressed that the opposite is true.

I am aware that many of these bearish statements are rhetorical, a passage in the annual ballet of the budget. It would be highly unusual for a friend of the NIH to complain that the agency is overfunded. Furthermore, many of the complaints are true. Additional funds ARE needed in a number of specific areas of the biomedical research enterprise, and academic institutions face financial problems on a number of fronts. But indiscriminate gloomy assessments of Federal funding for biomedical research

trouble me, for they fail to describe accurately the current state of affairs and they generate unnecessary pessimism. My opinion is based on the commitment of successive generations of strong champions of biomedical research in the Executive Branch, and in both houses of Congress on both sides of the aisle. They have been farsighted in recognizing Federal support of biomedical research as a sound and necessary investment of public funds. It must be added that the champions of our cause within the government could not have been nearly so effective had it not been for the unrelenting advocacy of the long term benefits of biomedical research by voluntary health organizations, professional and academic societies, and outstanding lay leaders of whom Mary Lasker is the archetype.

Thus, I am optimistic about the future of funding for biomedical research, if for no other reason than my conviction that key leaders in public life, industry and academia understand its essential role in our nation's future, and because public support for it grows ever stronger.





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ADDRESS\*

by

James B. Wyngaarden, M.D.\*\*

It is fitting that the theme of the 1988 Yankee Dental Congress--your 13th annual meeting--is "Heritage of Excellence." New England's cultural heritage is unparalleled in the nation. Some of America's greatest achievements in government, education, sports, science, medicine and the arts have emanated from your five great states. New England is also the home of some of the world's finest dental schools and research institutions, such as the dental schools at Tufts, Harvard, and Boston University, as well as Forsyth Dental Center. Furthermore, New England has nurtured some of the nation's most outstanding leaders in the Federal government--like Representative Silvio O. Conte here with us today.

This year's theme of "Heritage of Excellence" is appropriate for another reason as well:. It highlights the nation's heritage of excellence in biomedical research. I am particularly mindful of that heritage because we celebrated the centennial anniversary of the National Institutes of Health last year. All year long we took note of the progress that has been made, particularly in the last few decades, of what we recognize as a revolution in biology--a revolution that has amassed a spectacular store of knowledge, and that has forged the academic-private sector-government partnership in research.

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\*Address presented at the 13th annual "Yankee Dental Congress," New York, N.Y., January 24, 1988.

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Finally, the theme of this gathering is fitting because this year also marks the 40th anniversary of the National Institute of Dental Research--created by Act of Congress in 1948 as the third of the National Institutes of Health, and given the mandate to conduct research and training to improve the oral health of the American people. NIDR, too, has a strong record of research excellence. Its story is a chronicle of scientific breakthroughs that have had a profound effect on the practice of dentistry, not only in New England but throughout the world. Research on caries, periodontal disease, developmental anomalies, acute and chronic pain, restorative materials--are just a few of the many areas greatly influenced by NIDR during its 40 years.

It is this "heritage of excellence" in biomedical research that brings me here today. I want to talk to you about science--about the cascade of advances that are changing our lives as human beings and professionals. These changes affect every field of science--from astronomy to zoology, economics to electronics. But the impact of these changes has been most intensely and profoundly felt in the health sciences. At least, so it seems to me. We can hardly open the daily paper without reading about new conquests of old diseases, new technologies and treatments that promise a further prolongation of life, a steady increase in the life span, a gain in the quality of life. We are closer than ever to understanding fundamental life processes, unraveling the code of development, the enigma of aging, the mystery of selfhood and the marvels of the brain.

Dental research, of course, is a part of this wonderful enterprise, undergoing the most exciting period in its history. In the time frame of a single generation we have seen dental research mature, not only to become the driving force of dental education and practice, but also to become a full partner in biomedical research, enlarging its horizons and contributing to the solutions of the most challenging puzzles of all: how the human mind and body work.

Surely one of dental research's biggest victories--a revolution in its time--occurred in dental caries. The revolution began with the observation that people living in areas where the drinking water was naturally rich in fluoride sometimes developed a brown stain on teeth--but were resistant to tooth decay. By the 1940s, sufficient evidence had accumulated to persuade civic leaders to approve one of the most successful experiments in public health ever launched. At 4:00 in the afternoon of January 25, 1945, Grand Rapids, Michigan--my home town--became the first city in the United States to fluoridate its water supply.

Now we are seeing decades of investment in fluoride research pay off in remarkable declines in tooth decay. Almost 40 percent of American schoolchildren under 17 are caries-free; never had a cavity, never had a filling. And those who still have caries have only half as many cavities as their schoolmates a generation ago. Caries--a disease more common than the common cold--is for the first time in the history of mankind in decline.

Those figures are based on a nationwide survey of schoolchildren that the Dental Institute conducted almost 10 years ago. It is now replicating that study--with some additional data collection. Based on smaller surveys that have been conducted recently, it seems unlikely that we will see any reversal in the downward trends in caries prevalence.

When you combine that surmise about children's oral health with what the NIDR found in its national survey of working adults and older Americans last year, one can't help but conclude that we are witnessing spectacular gains in the nation's oral health. The adult survey showed that only 4 percent of workers aged 18 to 65 were edentulous. Half of the adult working population had lost, at most, only a single tooth. To be sure, adults still experience tooth decay. Nearly all of them have some form of periodontal disease, too. However, the signs and symptoms are generally mild.



The oral health of the seniors is more problematic. In contrast to the workers, 42 percent of those 65 and over have lost all their teeth. The older groups experience coronal caries at about the same rate as the younger-aged groups, but the prevalence of root caries was three times what was seen in the employed population. The seniors also have more severe and extensive signs of periodontal disease.

Clearly older Americans--the segment of the population that is already large and growing larger--will present serious challenges to the dental profession for years to come. Indeed, as NIDR continues to analyze the data from the adult survey and assess the new schoolchildren data, it may be that there are particular groups or individuals at all ages who for one reason or another are at high risk and unusually susceptible to disease.

For many Americans, however, the successes of dental research are paying off handsomely in improved oral health. It took another revolution in research to establish that the two major dental diseases were caused by bacteria in dental plaque. That knowledge immediately established that the diseases could be completely prevented--not just treated successfully. Now that information has been translated into dental practice, and, important, it has affected the behavior of the public. Americans have grown more sophisticated in matters of health and disease and they show an increasing readiness to adopt appropriate self-care and to seek professional help.

I believe that the two NIDR studies cited--surveys whose combined samples represent 150 million Americans--are of fundamental importance in shaping the dental research agenda for the year 2000. It is true that some special population groups, farm workers, military personnel, the unemployed, are not accounted for, but at last there is an up-to-date picture of the oral health of mainstream America. Moreover, it is a hopeful picture,

one that suggests that it is not wishful thinking to predict that some day edentulousness will be eliminated in America. That may not happen by the year 2000, but it will be a conspicuous goal and a part of the dental research agenda of the time. It is conceivable that within the next 3 to 4 decades--by the time that the youth of today reach the retirement years--that goal can be reached. When that happens, a myth of aging will have been reversed that is as old as civilization, a myth that Shakespeare himself perpetuated in his description of the last age of man: "sans teeth, sans taste, sans everything," and, for the first time in the history of civilization the lifetime of the human dentition will match the human lifetime.

In the years ahead there will be a need to conduct more detailed epidemiologic studies of selected populations; a need to study those who are healthy as well as the unhealthy; a need for more longitudinal and case control studies. With the increase in numbers of older Americans, we will need better information on them, as well as on the prevalences of systemic diseases and the use of medications that affect oral tissues. The other day a radio reporter commented on the fact that as the baby boomer generation begins to swell the number of 40-to-60-year-olds in this country, we can expect a sharp increase in the number of cases of diabetes. And how many diabetic patients--or their physicians--know about the oral health consequences of diabetes?

At NIH, the need for better information--especially in relation to mature Americans--is prompting the NIDR to expand epidemiologic and related activities. In addition, the health problems highlighted by the recent findings are contributing to a broad research agenda that will carry dental research through the nineties and beyond the year 2000.

With respect to caries and periodontal diseases, dental research will go after the high-risk individuals. In NIDR's new children's survey of 1987, researchers collected saliva samples

for bacterial analyses as indicators of caries risk. In future surveys other kinds of diagnostic markers in saliva and gum fluids may be available to test for periodontal disease activity. In the case of juvenile periodontal disease, sophisticated genetic linkage studies may provide answers to some of the outstanding questions--perhaps leading to preventive strategies or early treatment for young people at risk.

Diagnostic research today is benefiting from high technology developments in computer science and engineering. Investigators are perfecting techniques for 3-dimensional radiography--CT scans of the mouth. There are already clinical studies of the use of magnetic resonance imagery, digital subtraction radiography, and nuclear medicine techniques to detect early, subtle signs of periodontal and soft tissue disease. At an international workshop that NIDR held two years ago experts in Compton scattering, ultrasonography and other acoustic and mechanical methods forecast dental applications of these methods down the road.

Complementing high technology are the cell and molecular biology techniques that use cDNA probes and monoclonal antibodies for detecting oral pathogens or disease products. Some of these methods have already been marketed as kits dentists can use to detect microorganisms associated with caries and adult and juvenile periodontitis.

Research to develop safe, simple and effective interventions to reverse or prevent disease will grow in importance. There are already miniaturized oral devices that can be fitted to single teeth for the controlled release of fluoride. And there are powerful antibacterials for the treatment of early periodontal

disease. Now investigators are combining several agents and developing new compounds for use in slow-release devices or as "designer salivas." These multiple-acting compounds will prevent or arrest disease as well as enhance repair and regeneration.

Regeneration research should be high on the agenda by the year 2000 as researchers learn to single out the critical cells and regulatory factors involved in reconstructing oral soft tissue and bone.

Meanwhile, biomaterials research continues to set its own spectacular agenda and will go on developing novel and attractive synthetics. The goal will be to build in greater durability, better aesthetics and improved application techniques. By the year 2000 bonding to dentin should be routine. The "art" of dental implants should be firmly established on sound scientific footing by that time, and implants may very well replace removable dentures as the treatment of choice for replacing teeth--even single teeth.

Research on synthetic and metal restorative materials may face new competition by the year 2000, however. Over the next decade we will be seeing more and more research to map the tooth genome: to isolate and clone all the genes essential to the formation of the dental hard tissues--enamel, dentin and root cementum. Researchers have already cloned enamel genes.

What is interesting about that activity is not so much that dental researchers might learn how nature makes tooth enamel and then duplicate it in the laboratory--as promising as that might be. The real excitement lies in the contribution dental research could make to a goal that has been proposed for the biomedical research community as a whole: to map the whole human genome. As dental science's part in that ambitious process, it might attain understanding, at the most fundamental level, of the commands, the controls and the feedback operations that govern the



development of a unique organ--the human tooth. That knowledge should prove invaluable in understanding genetic diseases of teeth as well as shedding light on developmental processes occurring in other organs of the body.

That last example of proposed research for the year 2000 points to a development in dental research that has been implicit in much of what I have said, but surely will grow in importance and affect virtually every field of dental research. It is molecular biology--the use of recombinant DNA and monoclonal antibody techniques--in research. Without a doubt the pervasive mood of excitement, the rapid rate of progress, and the research accomplishments that are accumulating right now owe much to the widespread adoption of the techniques of cell and molecular biology by dental investigators.

Take the area of developmental biology. Dental research has a tradition of excellence in this field with outstanding research on craniofacial growth, congenital anomalies and wound healing. Not least among major accomplishments have been those achieved in the study of teratogens, cleft palate repair, speech rehabilitation, orthodontic studies, and blood clotting factors. With the infusion of molecular approaches, dental researchers are now discovering the critical roles of an increasing number of protein growth factors; they are delineating the structure and function of basement membrane molecules that control cell migration, proliferation, differentiation, repair and regeneration.

One byproduct of this research has been the development of a reconstituted basement membrane gel. Investigators are using this gel as a culture medium, a stimulant for nerve regeneration, and as a rapid assay of the invasion potential of cancer cells. Furthermore, this new knowledge is leading directly to the design of drugs to block metastasis.

Pain research is another area where cell and molecular approaches have been a boon in leading to a new understanding of the body's own pain control mechanisms. In turn, that understanding has led to the design and testing of new pain-relieving drugs. Dentistry has a proud tradition in this area, as we know. What is so gratifying is that dental reseachers continue to be leaders in the field, exploring all aspects of acute and chronic pain wherever it occurs in the body. Now, there are signs of increased activity in the field of orofacial sensory-motor activity. This seems to be a step in the right direction.

The dental community should expect increased attention to the oral soft tissues and salivary glands in the agenda for the year 2000 as well. An immediate spur to research is the AIDS epidemic, and the need to come to grips with the many oral lesions as well as subtle changes in the salivary glands that are associated with the syndrome. We would not be able to address these urgent concerns so readily, however, were it not for the fact that the oral mucosa present a special challenge to a new generation of virologists, bacteriologists, and immunologists who have entered dental research. Trained in molecular biology, these researchers seek an understanding, at the cell and molecular level, of the endless warfare that goes on in the oral cavity. Their goal is an ecological balance that favors the host. Toward that end these researchers are studying the natural history of AIDS, oral cancers and oncogenes and problems of latency and reinfection associated with the herpes family of viruses. Clinically, these investigators are close to human trials of several candidate herpes virus vaccines, some which use a synthetic antigen, others which are based on splicing herpes genes into a harmless viral carrier. I might add that oral medicine investigators are also making fundamental contributions to the science of biotechnology itself: They have developed a new method of generating human monoclonal antibodies.

I could continue to fill out the future research agenda with examples from mineralized tissue research and the work on collagens and proteoglycans, the discoveries of new bone growth factors and animal models of disease; I should also be emphasizing the growing importance of behavioral science research in reducing risk factors for oral diseases and in treating chronic pain conditions. Behavioral research will also become increasingly important as we focus on older-aged and high-risk patient groups. There will be a need to explore methods of coping and develop ways to change behavior to promote oral health and prevent disease. Equally important will be efforts to improve communication between patients and practitioners and the development of techniques to expedite transfer of research findings to the profession and the public.

But let me stop here and emphasize a few main points about a possible research agenda for dental scientists in the year 2000. The agenda should be informed by epidemiologic research for the obvious purpose of obtaining information on disease patterns and trends. On the other hand these trends should not dictate the research agenda. They should allow for new developments and unexpected findings that lead the gifted researcher down new paths. Not only do these researchers have to allow for such surprises, they need to cultivate a climate that encourages the special few who turn science in completely new directions.

To create that kind of environment requires a research agenda that is broader and deeper than ever, one that is invigorated by the new technologies, advanced equipment, and computer sophistication that fuels the modern research engine. In that environment science can stretch and grow, as it has historically. Science is by nature an expanding field. It progresses by ridding itself of outmoded ideas and accumulating new discoveries that seed the next advance. In terms of dentistry, dental research is the force that is rewriting its

history; dental research is changing the content of dental school curricula, and changing the way dentistry is practiced. The success of dental research in the past few decades, its continued rapid growth and gain in momentum will mean that we can expect an even greater impact on dental education and dental practice in the years to come.

These changes will not happen overnight. However, they are coming at a time when there has been some agitation on the part of the profession worldwide. It is certainly understandable for some to feel concerned. There ARE lowered application rates at U.S. dental schools; there ARE concerns about an oversupply of dentists. Let me say that, on the whole, I think that the dental schools are adapting to the situation well. They are making prudent decisions to ensure high standards and attract the best students.

Believe me, if dental science is going to get on with the challenges of a research agenda that suits the 21st century it will be to everyone's benefit to work together. It is all too easy these days to become fatalistic about the support of research: budgets are tight and competition tough. But we--even the good gray bureaucracy in Washington--are becoming more inventive. We are developing new kinds of awards, extending their length in time, and we are now encouraged to forge closer ties with the private sector--and so we are. We also are looking to global sources for support as well, working out new international collaborations and opportunities for Americans to work in foreign laboratories.

The take-home lesson here is that there's a wonderful world awaiting us by the year 2000. As Massachusetts' own Ralph Waldo Emerson wrote, "The past instructs: The future invites. I think his words are especially appropriate for the future of dental research.





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PROPOSED COMMENTS BY DR. WYNGAARDEN TO FIC ADVISORY BOARD

January 27, 1988

1. I have a personal interest in International Biomedical Research and therefore strong interest in programs of the FIC.
2. We are conducting an accelerated search for a new Director of the FIC. Dr. Kupfer is serving on the search committee. I hope I can make a selection in the next several months.
3. The question of exactly what should be the guiding philosophy of the FIC is the most important question facing this Center -- I would expect that the Board and the Acting Director will carefully think about this problem and provide me detailed input. I want to review your input and come back and have a fuller discussion about this point.
4. In the meantime, the Board has a good opportunity to begin addressing this problem as it develops its recommendation on how to proceed with the \$3.5 million international AIDS initiative. I and my office intend to be fully involved in the development of this program. I look forward to your ideas on this subject.



REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

NIH APPROPRIATION FOR FY 1988

o NIH 1988 Appropriation a part of massive Continuing Resolution passed and signed December 22, 1987.

o After deduction of 4.26 percent for deficit reduction, the total for NIH is \$6.67 billion, of which \$448 million is for AIDS research.

o Overall NIH increase over FY 1987 is 7.8 percent. Increase for all programs other than AIDS is 4.8 percent.

Increase for AIDS research is 77.4 percent. (AIDS increase was \$196 million. Increase for all NIH programs other than AIDS was \$286 million.)

o FY 1988 budget for NLM is \$68 million.

o Increase for NLM over FY 1987 is 9.7 percent.

" " NCI (w/o AIDS) is 2.8 percent.

" " NHLBI (w/o AIDS) is 3.0 percent.

" " NIH (w/o AIDS) is 4.8 percent.

o The Continuing Resolution specifies \$3.8 million of the NLM appropriation for the new National Center on Biotechnology Information. The legislation also includes language that requires the NLM to publicize the availability of its products and services.

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\*Presented at the National Library of Medicine Board of Regents meeting, NLM Board Room, Bethesda, Maryland, January 28, 1988.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



- o The Conference Report accompanying the Resolution called for 6100 new and competing renewal project grants, including grants for AIDS. The Reporting Committees directed the NIH to shorten the time for review and award of AIDS grants, contracts, and cooperative agreements.
- o The Conference Report referred to the fact that the Appropriation Bill itself made no reference to position ceilings, but reminded that "if employment levels (in the PHS) are reduced as responsibilities increase," the Committees will reconsider the matter of ceilings.
- o The President's FY 1989 budget is scheduled to be presented to the Congress about February 16.

#### REGIONAL MEETINGS

Meetings on the subject of "The Health of Biomedical Research Institutions" have been held in Los Angeles and San Francisco in November, and in New York and Boston in December. More meetings are scheduled in Dallas and Atlanta on February 18 and 19, and in Chicago on March 24.

- o The meetings are held under the auspices of the Advisory Committee to the Director:
  - to describe the broad political context in which NIH operates;
  - to dispel some of the popular myths concerning NIH budgets and programs;
  - to discuss the broad goals and strategies that condition and influence current and emerging NIH policies and practices; and
  - to encourage members of the scientific community to develop and maintain a keen awareness of the process by which science budgets are developed and to increase their active participation in that process.

And secondly:

- to solicit through public testimony the views of members of the

scientific community, university officials, and other interested parties concerning issues affecting the health of biomedical research institutions.

- o A full report on the results of the regional meetings will be made at the June 1988 meeting of the Advisory Committee to the Director.

#### THE "PRIVATIZATION" ISSUE

- o The plan for the privatization of the NIH, announced on the front page of the NEW YORK TIMES in early December, did not originate with NIH and was developed without our input or advice.
- o White House spokesman Fitzwater referred to the plan as a "trial balloon not fully fleshed out."
- o The privatization issue has received nationwide attention in the press. A number of editorials have appeared regarding the plan--all negative, some emphatically so.
- o I have responded to media queries that we see the proposal as at least an indication that the highest levels of government are aware of the problems we have had in recruiting and retaining the kinds of scientists we must have to maintain the high standards of excellence we require for our intramural program.
- o Acting on the premise that the problem should be studied, a proposal has been made that the issue of privatization be considered in a study by the Institute of Medicine of the National Academy of Sciences on the desirability of such options as making intramural NIH a freestanding government laboratory, a government-owned/company-operated laboratory, or continuing in the status quo.



## DEPARTMENT OF HEALTH AND HUMAN SERVICES

## National Institutes of Health

## Statement of the Director

Mr. Chairman, it once again is my privilege to appear before you and the members of the Subcommittee to present the President's budget proposal for the National Institutes of Health. Today I will report briefly on some of our activities and plans, and describe the highlights of the request for Fiscal Year 1989. In later statements the Directors of the constituent units of the NIH will present more details about our plans and programs.

It is always a pleasure for us to appear at these hearings because of the depth of information and constructive concern that you, Mr. Chairman, the members of the Subcommittee, and the staff have consistently shown in the programs of the National Institutes of Health. Because of the Subcommittee's interest in the NIH 100th anniversary, I am happy to report the completion of the year's full and varied schedule of centennial observances. It was our objective for the centennial observance that it would help create a better public understanding of the importance of biomedical research. Further, we expected that through the events we might attract the attention of young persons in such a way as to induce them to consider the value and satisfactions of a career in biomedical research. Without going into further detail about the centennial, I am pleased to report that the observance was an unqualified success.

Recently our principal program officials and members of our major advisory groups have been holding hearings in different parts of the nation on "The Health of Biomedical Research Institutions."



The meetings have been held in San Francisco, Los Angeles, New York, Boston, Dallas and Atlanta. One more is scheduled for late March in Chicago. The sessions are attended by members of the scientific community, university officials and other interested parties, whose advice we seek concerning current and emerging NIH policies and practices and any other issues affecting the status of the nation's biomedical research institutions. We consider our working relationships with extramural institutions to be of key importance because the productivity of the nation's medical research enterprise depends in large measure upon the health of the nation's biomedical research institutions.

I am pleased to report two appointments to major NIH positions during the past year. Dr. Katherine Bick had been named our Deputy Director for Extramural Research. Following a successful career in academia she has served with distinction for 12 years as a scientist-administrator at NIH. The other appointment was that of the first Director of the National Center for Nursing Research, Dr. Ada Sue Hinshaw. She came to NIH from the administration and the faculty of the University of Arizona's Health Sciences Center.

Among the research developments of the past year, I wish to call your attention to one in particular. It was the discovery by Dr. Michael Zasloff, of the National Institute of Child Health and Human Development, of naturally occurring substances that operate as a chemical defense system against microorganisms. While conducting research on an entirely different subject, he made a shrewd observation that surgical wounds on laboratory frogs heal infection-free even when the frog's environment teems with infectious organisms. This led to the discovery of "magainins"--naturally occurring chemicals that protect frogs and possibly humans

against infections. Our pleasure in referring to this exciting development is moderated by the fact that Dr. Zasloff will be leaving the NIH intramural programs to join the faculty of the University of Pennsylvania. While many factors usually contribute to such decisions, our ability to retain leading investigators is seriously compromised by the widening gap in the salaries and other benefits available to our senior scientists, together with various Federal administrative requirements, as compared with their counterparts in the academic community.

The Office of Management and Budget has taken note of the Federal administrative controls and procedures, including personnel procedures, space allocation procedures, congressional requirements, and the widening salary gap, that limit the capacity of the NIH intramural research program to sustain its distinguished record of scientific achievement and excellence. If the extraordinary accomplishment of the NIH intramural laboratories is to be assured over the long term, solutions must be found to these administrative barriers.

The Department of Health and Human Services has been encouraged by the Office of Management and Budget to consider a wide range of strategies for assuring the continued scientific excellence of the intramural program, and was advised to ask the Institute of Medicine to undertake a 4-5 month study of the options. Recommendations have been requested by June 1, 1988.

Throughout the scientific community new techniques in the manipulation of DNA and the development of new methods of automated processing of DNA are yielding large volumes of information regarding the human genome. Characterizing the entire human genome will have profound implications for understanding the more than

3500 diseases that are known to involve a genetic defect. This knowledge will enhance our understanding of the normal processes of development by many fold.

Every day brings new information on the location of genes. The locations of new markers, particularly those in close proximity to genes associated with known genetic disorders, are published in each issue of the leading scientific journals. Information on the location of individual genes will become known through the course of normal scientific inquiry, but if we are ultimately to succeed with this project we must capture information systematically for the construction of the complete map. The staggering volume of molecular data and its cryptic and subtle patterns have led to an absolute requirement for computerized data bases and analytical tools if we are to succeed in this major advance. Based on recommendation of this Subcommittee, an amount of \$3.8 million was included in the FY 1988 appropriation for the establishment of a National Center for Biotechnology Information at the National Library of Medicine. Working with the laboratories from which the information comes, experts at such a center will seek to coordinate data as it is accumulated--to store, process, and make it available to the research community nationwide.

Permit me to mention a few highlights from recent research activities.

- o A major study supported by the National Institute of Child Health and Human Development has concluded that the drug cysteamine can prevent kidney failure and permit normal growth when given to very young children who inherit the rare metabolic disease cystinosis. This represents the first

effective therapy for any of the genetic disorders known as lysosomal disorders.

- o Earlier this year, a prevention study supported by the National Heart, Lung, and Blood Institute showed that one aspirin tablet taken every other day significantly reduces the incidence of fatal and non-fatal heart attacks in men who had no history of heart attacks.
- o Advances made by intramural scientists from the National Institute of Allergy and Infectious Diseases are rapidly moving us toward the development of a vaccine against rotaviruses, the most important cause of severe diarrhea--sometimes leading to death--among young children.
- o Scientists supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases have recently discovered that an immunosuppressive drug, cyclosporin A, is highly effective in the treatment of psoriasis, a chronic skin disorder. This discovery--in addition to the evidence showing that a high percentage of HIV-positive patients have symptoms of psoriasis--redirects scientists to look more closely at the possibility that psoriasis is an immune disorder.
- o During the past year, studies supported by the National Cancer Institute developed the first highly effective regimen for advanced bladder cancer, a cancer that affects nearly 50,000 Americans each year. In a study of combined chemotherapy using four drugs, there was an overall response rate of 70 percent in advanced bladder cancer, with 37 percent of patients having complete remission.



The NIH has a major research commitment in AIDS. Sixteen NIE components, stressing research in pathogenesis, therapeutics, and vaccine development, are involved. To assist in setting research priorities for AIDS research at NIH, I recently established an AIDS Program Advisory Committee with membership drawn from the country's most distinguished scientists, administrators and ethicists. Another new development in AIDS is our program to speed the review and award of AIDS grant applications. The plan will be announced to the scientific community shortly.

Intramurally, we recently expanded NIH's capacity to conduct clinical research on AIDS patients through a new allocation of beds at the NIH Clinical Center for additional Phase I drug studies. Our intramural and extramural efforts in the areas of drug and vaccine development continue. The first Phase I study of an AIDS candidate vaccine in this country began in October at the NIH Clinical Center, with additional candidate vaccines moving toward testing in our network of Vaccine Evaluation Units.

In the treatment area, various drugs and combinations of drugs are being studied both at the NIH and through the AIDS Clinical Trials Group (ACTG) around the country. One of the most promising treatments being studied is a combination of AZT and a related drug dideoxycytidine, both pioneered as AIDS therapies at the NIH. We also have just begun a trial of trimetrexate as an experimental drug for treatment of pneumocystis carinii pneumonia patients who suffer serious adverse reactions to the existing approved medicines. In addition, trimetrexate will be distributed as a "treatment investigational new drug" through the National Institute of Allergy and Infectious Diseases. NIH's program to apply techniques of

structural biology to the design of new drugs for the treatment of AIDS has begun.

The FY 1989 funding request proposes consolidation of funds for AIDS in the Office of the Assistant Secretary for Health. The amount identified for NIH is \$587.6 million, an increase of \$119.8 million or 26 percent over the FY 1988 estimate. Detailed descriptions of the AIDS research conducted and supported by the various NIH components are contained within the individual budget justifications and in the PHS consolidated submission.

Mr. Chairman, the FY 1989 budget request for the National Institutes of Health is \$6,535.2 million, an increase of 5.4 percent over the comparable FY 1988 level of \$6,198.9 million. For comparability with FY 1989, funding for acquired immunodeficiency syndrome (AIDS) is excluded from the FY 1988 total.

The FY 1989 request will support a total of 20,600 research project grants, the largest total number of research grants ever awarded by NIH, 837 more awards than the FY 1988 comparable level. The total number of research project grants, excluding AIDS, is made up of 14,989 noncompeting continuations and 5,611 new and competing renewal awards.

The President's request would allow average cost increases for research project grants of about 4.7 percent for noncompeting awards and 2.9 percent for competing awards.

The FY 1989 request for research centers, \$539.2 million, would provide support for 555 centers, three fewer than under the current budget. General clinical research centers would receive a two percent increase. Average costs for all other center grants would be approximately the same as the FY 1988 level.

Research training and career development activities would remain close to their FY 1988 operating levels with an increase of 3 percent for research career programs and a 2 percent increase for research training.

The NIH intramural research program would receive \$670.6 million, an increase of 3.7 percent over the FY 1988 comparable level. The additional funds would be used to support built-in increases.

Mr. Chairman, this completes my opening statement, but I will be pleased to respond to any questions you or members of the committee may wish to ask.

STATEMENT BY

JAMES B. WYNGAARDEN, M.D.

DIRECTOR

NATIONAL INSTITUTES OF HEALTH

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT

OF THE HOUSE COMMITTEE ON ENERGY AND COMMERCE

FEBRUARY 22, 1988



STATEMENT OF JAMES B. WYNGAARDEN, M.D.  
DIRECTOR, NATIONAL INSTITUTES OF HEALTH  
BEFORE THE  
SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT  
OF THE HOUSE COMMITTEE ON ENERGY AND COMMERCE

Mr. Chairman and Members of the Subcommittee:

I am pleased to present this testimony on the role of the National Institutes of Health in biotechnology information. Although examples of biotechnological innovations span 200 years, the contemporary field of biotechnology, with its enormous potential benefits for human health, owes its existence in large measure to the sustained research support provided by NIH in the form of grants to medical scientists. Many of the more than 70 Nobel Laureates who have been supported by NIH funds have received their honors for work related to biotechnology. For example, NIH's own Dr. Marshall Nirenberg was recognized by the Nobel committee for his work in deciphering the basic "genetic code."

The NIH continues to place high priority on biotechnology-related research, both at our own laboratories in Bethesda and through grant support of individual projects at research institutions around the country. Among the subjects of investigation are: understanding cancer and genetics, clinical immunology and allergic responses, and disease prevention through vaccine production. Biotechnology research has already made possible the large-scale production of therapeutically useful substances such as insulin, interleukin, growth hormone, blood coagulation factor VIII, and tissue plasminogen activator (tPA), now approved by the FDA for commercial release.

The importance of biotechnology research is underscored by the fact that an entire meeting of the Advisory Committee to the NIH Director was devoted to the subject. The committee heard from many outside experts and concluded that

if the United States was to continue its preeminence in biotechnology, the NIH should continue to support basic biomedical research and research training in the field. In another meeting of the advisors, on the subject of "Characterizing the Human Genome," the crucial role of the NIH in gene mapping and gene sequencing was emphasized. This time, however, they made the explicit point that we have a major problem with handling just the biotechnology information being produced by our present level of effort. As our laboratories generate ever greater amounts of data, we will need ever more capable information-handling systems. We are addressing these issues with funds appropriated for fiscal year 1988 and funds requested in the President's 1989 budget.

NIH already funds about a dozen major computerized biotechnology databases, each with its own characteristics. Among them are the Hybridoma Data Bank, ATCC Cell/Tumor Bank, the Human Mutant Cell Repository, the Human DNA Probe Repository, Human Gene Library, Protein Information Resource, and GenBank. In addition, other countries support the European Molecular Biology Laboratory (EMBL) Bank of Nucleic Acid Sequences and the DNA Databank of Japan.

The Library's role will be to coordinate and enhance these various information resources for the benefit of individual scientists throughout the United States. This will be done using modern electronic networking technology and what are called "distributed databases." In effect, this means that biotechnology databanks can remain physically where they are at present, scientifically directed by experts at universities, consortia, and corporations.

This is especially appropriate because the information/communications function of NIH, exercised largely through the National Library of Medicine, is vital to our entire biomedical research enterprise. The programs of the Library in collecting, classifying, and disseminating information are the building blocks for future research advances and improved health care delivery. These vital information-handling services, enhanced by such promising new programs as the Unified Medical Language System, are absolutely necessary for optimal progress in biotechnology.

In keeping with its role as the principal source of Federal support for biotechnology research, the NIH also participates in several activities that cut across agency boundaries. For example, I am chairman of the Biotechnology Science Coordinating Committee (BSCC), which operates under the aegis of the White House Federal Coordinating Council on Science, Engineering, and Technology (FCCSET) Committee on Life Sciences. Other members of this Committee include Federal agencies that support biotechnology research, and those with a regulatory responsibility. These are, in addition to NIH, the National Science Foundation, the Food and Drug Administration, the Department of Agriculture, and the Environmental Protection Agency. The mandate of the BSCC is to consider the scientific issues relevant to biotechnology and to share information used to support biotechnology regulatory activities. Clearly, our plans for the Center will enhance the ability of NIH to make this a productive effort.

In addition to existing NIH support for biotechnology research, the importance of the field was underscored just two weeks ago with the release of a major

report, "Mapping and Sequencing the Human Genome," issued by the National Academy of Sciences. The report recommended that a 200-million-dollar-a-year effort be begun immediately to discover the location of every gene within human chromosomes. In fiscal year 1988, the NIH has received \$17.3 million of new monies specifically for funding a new research program in mapping and sequencing complex genomes. The President's Budget request for NIH for fiscal year 1989 increases this amount to \$28 million. These funds will support a scientific approach that is very different from existing work on complex genomes. Until now the approach has been to identify specific genes of interest, to locate them on the appropriate chromosome when possible, to isolate, clone, and sequence them. The genes that have been of special interest have been those that have controlled the structure of known substances, such as insulin or growth hormone, or have been responsible for certain hereditary diseases, such as sickle cell anemia. NIH devotes about \$100 million a year to projects in human genetics and genetic diseases and an additional \$200 million per year to other studies of complex genomes in animal models. A portion of these sums is spent on mapping and sequencing, but it is important to stress that the existing approach focuses on a limited number of widely scattered genes. There are millions upon millions of nucleotides that will not be identified by the traditional approach. The new program and the dedicated funds in the '88 and '89 budgets will seek to locate genetic markers at shorter and shorter distances along the entire stretch of the chromosomes, and ultimately to define the structure at the level of the individual nucleotide sequences.

Mr. Chairman, I would like to close by reiterating my strong support for making an effort not only to develop new and improve existing information



resources, but to forge sophisticated communication linkages between resources, particularly databanks, so that researchers can have rapid and efficient access to all the scientific information that is relevant to their investigations. Funding a National Center for Biotechnology Information was a right step to that end. Efforts will continue under the President's FY 1989 budget request. As you will hear from Dr. Lindberg, we have already begun to see the results of stepped-up work in developing improved information services for biotechnology.

Mr. Chairman, members of the Committee, this concludes my prepared statement. I will be pleased to answer questions.

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# NURTURING THE BIOMEDICAL RESEARCH ENTERPRISE

by

James B. Wyngaarden, M.D.\*\*

I am honored indeed to have been selected to give the Theobald Smith Lecture--and more than pleased to become a member of the group of distinguished persons who have preceded me in carrying out this tradition, particularly two of my most deeply respected former colleagues at Duke--Phil Handler and Gene Stead. It is singularly appropriate that the Theobald Smith Lecture be a part of the first academic symposium to be held in connection with the Albany Medical College Sesquicentennial observance. For Dr. Smith, an 1883 graduate of Albany Medical College, personified the awakening of science in this country that took place in the latter part of the nineteenth century. While in Medical School he became deeply interested in the works of Robert Koch and the new science of bacteriology. Very soon after his graduation he collaborated with Daniel E. Salmon in identifying the microorganism that causes hog cholera. They were the first to discover that immunity could be conveyed by dead bacteria.

Dr. Smith soon was at the forefront of the investigators of his time, gaining recognition as the first to prove that disease could be transmitted by an insect when he identified the tick as the intermediary of transmission of the cattle disease known as "Texas fever." This principle in time came to have great significance in the control of human disease. It once was said of him that his admirable contribution is an illustration of the unity of comparative and human medicine. From another perspective his career provides an example of unification as commented upon by Rene Dubos who said, "For the sake of scientists who tend, or pretend, to despise abstract concepts and to have respect only for hard facts, it is worth pointing out that the most abstract formulation of the problem of parasitism first came

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\*Address presented at the 1988 Theobald Smith Lecture,  
Albany Medical College Sesquicentennial Symposium,  
Albany, New York, March 10, 1988.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

first came from the American pathologist Theobald Smith, who more than any other American scientist contributed important hard facts to microbial knowledge."<sup>1</sup>

As this institution observes its 150th birthday, I am sure you will take special pride for having nurtured young Theobald Smith's interest and imagination.

Only a few weeks ago the National Institutes of Health held the closing events of its centennial year, so I am somewhat attuned to the feelings you must have as you begin celebrating the sesquicentennial of Albany Medical College. Personally and on behalf of my NIH colleagues, I extend warmest greetings and congratulations to the faculty, staff, students and friends of Albany Medical College as you mark a significant anniversary in the history of this distinguished institution.

Albany Medical College was already in its fiftieth year when a tiny laboratory that later became the National Institutes of Health was opened in New York City. The NIH had its beginning when a young physician, Dr. Joseph Kinyoun, opened a one-room laboratory in the Marine Hospital service facility on Staten Island. Dr. Kinyoun had been given special training in the new science of microbiology in the laboratories of Robert Koch and Louis Pasteur. He had also been given an assignment--to learn and apply the latest in scientific insight in an effort to forestall a threatened outbreak of cholera in the United States. As the years have gone by, the mission of the NIH has been expanded step by step so that today the scope of its research extends across the total spectrum of the sciences, and through its extramural programs the NIH is in active partnership with essentially all institutions involved in biomedical research, including Albany Medical College.

Both of our institutions have experienced at first hand a period of astonishing advances in knowledge, and particularly in the biological sciences. Even more exciting is the promise that the future holds. As a preface to a discussion of some of the issues of concern to the research

community and their possible impact on the future, I will refer to a few chapters in the history of the National Institutes of Health.

What we call the modern NIH had its beginnings at the end of World War II. Essentially all of the American bioscientists and clinical researchers had been mobilized in the war effort. This mobilization was accomplished by awarding grants and contracts to American academic institutions, hospitals, and independent laboratories for the conduct of research on health problems that were expected to be encountered by the members of the armed services. Some 500 such awards were made during the war years. About 250 medical projects were still active when the Office of Scientific Research and Development was disbanded in 1945. These ongoing projects were turned over to the then National Institute of Health for administration.

That action and the policy decisions that preceded it put in place, for the first time, a broad Federal program for the support of biomedical research that was not linked to wartime necessity or to a specific disease. The action also had the effect of designating the NIH as the principal biomedical research arm of the Federal Government.

The idea of a general and continuing research partnership through grants and contracts awarded by the Government to non-Federal institutions was a new thing. No patterns existed for it; but in little more than a year after the passage of the authorizing legislation, a system was set in place that has stood the test of time and has served as a model for organizations over the world. This largely unsung accomplishment was substantially the work of C. J. Van Slyke, then Chief of the Research Grants Division and later NIH's Deputy Director. His philosophy regarding the research grants program was a total commitment to the basic tenet that such a system should protect the integrity and the independence of the research worker and his freedom from control, direction, regimentation and outside interference. He insisted that the projects to be supported be selected in open competition, and that in making decisions on awards the agency should rely to a substantial degree upon appraisals by non-Federal scientists. Thus the system was designed to utilize in a significant way the expertise of



scientists throughout the nation not only in the conception and conduct of the research but also in the evaluation of research proposals.

Forty years later we continue to avoid central direction of research when it is at all possible to do so. My personal philosophy is that the most important thing the NIH can do over the years is to promote discovery. No study section or advisory committee or review board can sit around a table and say "now it's time to discover penicillin" or anything else. Our successes come from supporting good scientists and giving them freedom.

While recalling some of the influences on research that have not changed greatly over the years, I will digress to mention another matter that has been a constant companion of biomedical research over the years and was of concern to Theobald Smith. It is the effort by small, often unrelenting groups to put an end to the use of animals as subjects of research. I was interested to note in a biography of Dr. Smith that he was appointed in 1896 to a small committee by the Association of American Physicians to oppose a bill to prohibit vivisection in the District of Columbia. The bill failed but the general issue remains. It has become highly politicized, and stepwise has effectively increased the cost of research through unreasonable application of meritorious reforms in standards for animal care and curtailment of the use of pound animals. In some areas of research the problem goes beyond expense. For example, the scarcity of chimpanzees already threatens development of a vaccine for AIDS, and any unnecessary restrictions on their use at this time becomes doubly serious.

But I must return to my sketch of NIH history. The rapid expansion of the NIH organization has mirrored public concern about specific diseases and general categories of health problems. The names of the twelve Institutes constitute a kind of catalog of such concerns, as can be seen in the names of the National Cancer Institute, The National Heart, Lung, and Blood Institute, the National Institute of Neurological and Communicative Disorders and Stroke, and the National Institute on Aging. Although many of the Institutes were given disease-specific missions, our commitment to basic research has been sustained and is a substantial component in the

programs of each of the Institutes. In the early 1970s, the fraction of the NIH budget devoted to basic research was no more than 45 percent. By 1980 this portion had reached 52 percent, and in 1986 it was 63 percent.

During recent years between 10 and 12 percent of our total budget has been spent for intramural research and training in NIH's own laboratories. About 2,500 scientists with doctoral degrees and as many as 3,500 trained support staff are engaged in our intramural programs.

Since the early 1950's, large numbers--an estimated 25,000--of young scientists have come to the NIH under our fellowship and associate programs for periods of from a few to several years, and then they have moved on to universities, academic medical centers and industrial organizations. We believe that these NIH alumni enrich American science. The linkages that develop between scientists working together in the intramural programs at NIH often are lasting. As a rule, scientists who move from NIH continue to collaborate with their former NIH colleagues, they return for seminars, or they invite NIH scientists to visit them in their extramural setting so that there is a pattern of continuous interaction and collaboration.

As large as the intramural program is, however, almost 90 percent of the NIH's budget is devoted to our extramural programs--to awards for research and research training and for the associated administrative costs. Thus, the largest amount, by far, of NIH research takes place in some 1650 universities, medical schools, research hospitals, foundations and industrial laboratories in the United States and in many other countries. More than 50,000 non-Federal scientists participate in research projects funded by the NIH.

The NIH has had a marked influence on the structure as well as the quality of academic institutions, not only through the large amounts of funds the agency has awarded for the support of research and research training, but also through the infusion of the able and well-trained alumni of our intramural programs. The building of many great research-oriented universities has rested heavily on NIH support, and currently more than 63 percent of all the health-related research in American universities and

about 75 percent of all research in academic health centers is funded by the NIH.

The key mechanism used by NIH for support of biomedical research is the investigator-initiated project grant. Such grants are awarded in response to proposals submitted by researchers who outline the questions they wish to study, who specify their research strategies and estimate their costs. Such grants are used for supporting the major portion of our extramural research. Well over half, or more than 58 percent, of our total proposed budget for FY 1989 is allocated to these projects.

But continued availability of a supply of high quality scientists is essential to the nurture of the biomedical research enterprise. In science the limiting factor is a human one. Thus it is our special responsibility as scientists, academicians and administrators to help assure the future supply of trained scientists. That responsibility cannot be met simply by organizing and funding more training programs. In science there is a long tradition of the nurture of young minds and imaginations that goes beyond conveying information and teaching skills. Theobald Smith made a telling comment on the nature of the scientist. "Let us not deceive ourselves concerning the true inwardness of research," he said, and explained, "It does not consist in trained senses alone. It is a quality, an attribute of the intellect working through the senses."<sup>2</sup>

A consequence of the amazing progress that has been made by the current generation of scientists is the level of sophistication that will be required of their successors. In the biological sciences there has been a substantial broadening of the scope of research. We have totally new disciplines within the biosciences so that larger numbers of more highly trained investigators will be needed if we are to continue the pursuit of discovery in new areas, such as structural biology and molecular genetics.

The Government-University-Industry Research Roundtable, of the National Academy of Sciences, has been holding thoroughgoing discussions of the issues relating to the development, identification, recruitment and retention of science and engineering talent. In evaluating the talent pool they

predict that the demand for scientists and engineers will remain strong in both industry and academia, but that at the same time the number of Americans qualified for these careers may be declining.

This prediction is based in part on certain disturbing trends. First, the supply of 22-year-olds is projected to drop more than 25 percent before the end of the century. If even the current level of supply for industry and academia is to be maintained, a significant increase in the proportion of 22-year-olds attaining science and engineering degrees will be necessary. The Roundtable group estimated that to maintain the 1985 level into the 1990s the degree award rate would have to increase by 30 percent.

A special problem is posed by indications of shortages of competent science and mathematics teachers in secondary schools, and with the evidence of the lack of achievement of U.S. students in mathematics. This has serious implications in the biosciences as well as in engineering.

A substantial drop in the number of baccalaureate degrees in the life sciences that began in the late 1970s continues unabated and portends shortages. Although the number of women and minorities is on the increase their numbers do not make up for the losses. All applications to U.S. medical schools declined in the 1987-1988 academic year, and according to a recent report first-time enrollments fell for the sixth year in a row.

There also has been a persistent decline in the number of younger applicants for traditional NIH grants. More than 26 percent of all applicants were under 36 years of age in 1979, but seven years later only a little over 13 percent were under 36. On the average, NIH-supported investigators are older today than in previous years. The average age in 1979 was 41.9 years, and in 1985 it was a full year older--42.9 years.

Given the demographics of the last decade of the 20th century, it is abundantly clear that if the necessary talent is to be available for continuation and extension of the explosive progress in the biological sciences, we must attract a greater share of the young people in these fields. Serious attention must be given to finding ways to develop the



abilities and interests of children in grade school. The early years are critical.

Secondary school is the period when decisions can begin, and the choices made in high school become crucial with respect to future careers.

The undergraduate years take a heavy toll in the numbers of students who elect to pursue careers in the sciences. When the time comes for them to decide whether or not to go into graduate or professional school, we must recognize that a decisive factor is the student's perception of the opportunity offered by a particular career, versus the investment in time and dollars required to prepare for such a career.

Because the NIH is the source of funding for almost two-thirds of the biomedical research conducted in American universities, our programs have come to be regarded as indicators of the level of biomedical research activity in the nation. For this reason we have stressed in our budget discussions with the Congress and within the Administration the importance of stability in funding of research project grants. A reasonable degree of predictability of research support is essential for institutions and for individual investigators if they are to attract and maintain productive teams of researchers. Furthermore, such stability can indicate to young people at critical stages in their careers that there is reasonable assurance that having completed the intensive training that today's science requires, they will be able to look forward to active careers in health related research.

In recent years the number and quality of research proposals have increased steadily and have outstripped our ability to fund them, even though the NIH budget has continued to grow in real terms by 2 percent per year since 1965, and 4 to 6 percent per year in the past 5 years. We now can fund only about one-third of the meritorious proposals.

The system is stable and morale is high as long as our annual appropriations permit a reasonable number of new awards each year in addition to providing for the continuing grants, whose average term is between 3 and 4

years. But the amount of funding available for new awards is subject to both the level of continuing commitments and to the level of new appropriations. Essentially the amount available for new awards is what is left after continuing commitments are met. In times of constrained budgets a roller coaster effect can develop with regard to new and competing renewal grants, and this in turn can send minor panic through the system. We have not yet developed a means for "buffering" current and prospective grantees from the effects of sudden budget changes.

It is essential to the vitality of the scientific enterprise and to the morale of the scientific community that young scientists be encouraged. In 1986 we announced a new program called FIRST awards--a modification that lengthens the initial awards from three to five years, and provides a total of \$350,000 direct costs for the five years. This is intended to obviate the need for too early reapplication for investigators who encounter difficulties in the first 18 months of the term of a grant. It will, we believe, encourage more creative and less defensive research applications.

Further, we have expanded the number and types of longer term support for outstanding mid-career scientists through a program called MERIT awards. This program will involve facilitated extensions of five-year awards for an additional three to five years on the basis of a detailed progress report rather than through reapplication.

Notwithstanding our efforts to fine-tune the system, the level of funding continues to be the principal determinant of our ability to nurture the productivity of biomedical research in the United States. We are especially concerned about the effect on the young researcher, who after seven to ten years of post college training has about a one in three chance of gaining independent funding from NIH.

We cannot quantify with precision how many decide to consider a change in their career path in the face of such odds, but there are indications that our concerns about this problem are justified.

In this connection it is pertinent to note that the President's budget request for Fiscal Year 1989 for NIH would support a total of 21,100 project grants. This is 960 more than the number of grants during the current year, and more than twice the 10,175 project grants we funded in 1970.

Within the portion of the budget that makes provision for project grants, the amount available for new and competing renewal proposals is a critically important element. The FY 1989 President's budget would permit a total of 5,761 new and competing renewal grants as compared with 6,052 that we estimate will be made during the current year.

A total of \$613 million is identified for AIDS research at NIH, and this represents an increase of \$164 million over FY 1988. The FY 1989 total for NIH would be \$7.123 billion, an increase of 6.8 percent over 1988, with 78 percent for AIDS research and 5.4 percent for all other research over the comparable 1988 figure.

The NIH continues to make a major commitment to the future of biotechnology. The portion of our budget devoted to biotechnology has increased gradually over the past five years, and about 14 percent is now devoted to directly related research, and about 35 percent devoted to underlying basic research and research training related to biotechnology. The training activity is of key importance, for one of the most crucial issues facing the biotechnology industry is the dearth of appropriately trained scientific personnel. The NIH spends \$60 to \$70 million a year to train research scientists in skills related to biotechnology. However, the supply of scientists who possess general knowledge in the areas of molecular biology, molecular genetics, chemistry, virology, immunology and biophysics is rapidly being outstripped by the needs of academia and industry. A 1985 survey of 138 American biotechnology firms by the National Academy of Sciences indicated that half of the respondents were experiencing a problem with the shortage of scientists. Moreover, as these firms recruit the best scientists from academia, there is a growing shortage of teachers to prepare the next generation of basic biomedical scientists.

I wish to emphasize how important I feel it is that adequate numbers of able and well trained scientists be available for the foreseeable future needs. The situation is critical with respect to molecular and structural biologists, not only as to numbers but also as to breadth, depth, and overall excellence of training. If this nation is to maintain its competitive position both in science and industry this need must be met.

Throughout the scientific community new techniques in the manipulation of DNA and the development of new methods of automated processing of DNA are yielding large volumes of information regarding the human genome. Characterizing the entire human genome will have profound implications for understanding the more than 3,500 diseases that are known to involve a genetic defect. This knowledge will enhance our understanding of the normal processes of development by many fold.

In the NIH appropriation for FY 1988 an amount of \$17.3 million was earmarked for the genome mapping project, plus an additional \$3.8 million for establishment of a related biotechnology information center at the National Library of Medicine. The President's request for FY 1989 includes \$28 million for the mapping and \$4 million for the communications center. Through the 1988 appropriation and the FY 1989 President's budget, both the Congress and the Administration have sent a clear message that this is an important mission, that there are immediate and long-range implications for public health, and that mapping the human genome should begin at once.

An expert committee of the National Academy of Sciences has urged an immediate beginning of a program to discover the location of every gene within human chromosomes. In a statement accompanying their report the Academy's committee stated its strong belief that "Such a special effort in the next two decades will greatly enhance progress in human biology and medicine." They also emphasized the need to study the genetic make-up of other animal species to provide comparative data.

This year on February 29 we assembled an ad hoc program advisory committee of some of the nation's outstanding leaders in the biosciences to discuss in some detail priorities and principles to be applied in carrying



out a major NIH program for mapping and sequencing the human genome. The ad hoc committee unanimously endorsed our plan to establish an Office of Research on the Human Genome, headed by a new Associate Director within the Office of the Director of NIH. The new office will have a coordination and integration function with regard to new as well as ongoing efforts within all components of NIH. The office will have responsibilities for development of new proposals as well. We will take steps at once to the formal chartering of an NIH Program Advisory Committee on the Human Genome. We intend to tap the best minds in the related disciplines in order to develop scientific plans and administrative options for promoting rapid progress in methods in mapping and sequencing, and for managing the wealth of information emanating from these studies.

With the enactment of the FY 1988 appropriation and the President's FY 1989 budget request, we feel confident that we can proceed with the highly important human genome project without risking the possibility that it would become a competitor and siphon funding from our other vital programs.

In biotechnology, as well as in all other areas of our activity, the NIH is committed to adding to the fundamental biomedical knowledge base and to ensuring that this knowledge is translated into applications that will improve the health of the nation as well as aid in its economic growth. For what the biosciences yield enhances the well-being of people here and, in fact, in all parts of the world. A broad description of the role of science in the life of people everywhere appears in an inscription within the dome of the Great Hall of the National Academy of Sciences in Washington. It reads "...To Science, Pilot of Industry, Conqueror of Disease, Multiplier of the Harvest, Explorer of the Universe, Revealer of Nature's Law and Eternal Guide to Truth."

Within science and technology the search for new measures for the diagnosis, treatment, and especially the prevention of human disease and disability is of preeminent concern, and our nurture of the biomedical research enterprise will continue to be of surpassing importance to the success of that enterprise.

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STATEMENT

BY

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DIRECTOR

NATIONAL INSTITUTES OF HEALTH

PUBLIC HEALTH SERVICE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON ENERGY AND COMMERCE

SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT

HOUSE OF REPRESENTATIVES

MARCH 15, 1988



Mr. Chairman, it is a pleasure to appear before you and the members of this Committee to discuss the issue of the AIDS research infrastructure. I am accompanied today by Dr. Anthony S. Fauci, NIH Associate Director for AIDS Research and Director of the National Institute of Allergy and Infectious Diseases. The points I wish to make today also apply to the research programs of our sister agency, the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA), through its components, the National Institute of Mental Health (NIMH), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the National Institute on Drug Abuse (NIDA).

The urgency and gravity of the AIDS epidemic demand even greater attention to NIH's exercise of its role in identifying and marshalling the biomedical resources and talent necessary to combat this disease. We appreciate this Committee's leadership and support since the emergence of the AIDS epidemic and are gratified that the Congress has taken such an active role in addressing AIDS research resource needs.

Nearly 7 years have passed since initial reports of a unique disorder that was eventually identified as AIDS reached the Centers for Disease Control. During that period, the NIH AIDS research budget has grown rapidly and our AIDS program has expanded into an extremely complex set of research activities. As you would imagine, this rapidly expanding program has placed a strain on the research resources, both human and material, that serve as the matrix for this effort.

Given our unfolding appreciation of the potential risks associated with HIV research, members of both the intramural and extramural biomedical research communities need access to the high quality facilities designed specifically for working with such hazardous pathogens. Further, as the nature of the AIDS research program evolves, so do the underlying resource needs. At present our greatest facilities needs are special laboratories for working with the virus, clinical facilities for drug and vaccine testing, and special animal facilities.

While full-time equivalent positions (FTEs) are available, NIH continues to experience difficulty in recruiting and retaining highly skilled medical and research staff and in replenishing our pool of investigators through research training opportunities. This is true in all areas as well as in those related to AIDS. To the extent possible we have been taking every opportunity to address these concerns, and we are making progress. As a compliment to NIH's ongoing assessment of our personnel requirements, the President's FY 1989 budget also calls for HHS to evaluate strategies to assure the continued scientific excellence of the NIH intramural laboratories. We will be asking IOM to undertake a 4-5 month independent study of a range of topics, including adjustments to the structure of the intramural research effort, based on the principles of academic research centers; modify the personnel system to permit an interchange between NIH research, private biotechnology researchers, and nonprofit biomedical research centers; continuation of the status quo; and other organizational and managerial changes.

The AIDS research effort has been supported strongly by this Administration. Since 1981, the Congress has provided substantial escalated and continuing support for the NIH AIDS program, and in fact, over the last 4 years, the amount appropriated for AIDS has nearly doubled each year. The FY 1989 NIH AIDS request is \$587,130,000, an increase of 26 percent over the 1988 estimate. The FY 1989 ADAMHA request is \$177,617,000. Similarly, there have been substantial increases in personnel allocated to the AIDS effort. The increases just since 1987 are illustrative. The number of FTEs dedicated to the search for the cause and cure of AIDS was nearly 400 in FY 1987, a fifteen-fold increase since FY 1982. That number will jump to 539 in FY 1988 and to around 600 in FY 1989. An increase of 100 FTEs in FY 1988 was provided through the FY 1989 budget process, and I have just allocated an additional 29 because of the ever-widening requirement of the AIDS research program. In addition to expanding the intramural research program, the increases in FY 1988 will provide resources to begin implementation of an accelerated awards process for AIDS grants, contracts, and cooperative agreements; to open the 12 East patient care unit in the Clinical Center; to expand the safety and support services related to AIDS; and to establish the Office of the Associate Director for AIDS Research in my office. All of these efforts are currently under way and represent an intensified commitment to all aspects of the AIDS research program.

There is still no cure for AIDS and no vaccine to prevent it. The extent of spread into the various populations and the timeframe regarding conversion from viral exposure to systemic disease and full-blown AIDS are not yet certain. An ideal animal model for vaccine testing is not available. Further research is essential. Aside from the specific scientific needs, there are new and previously unanticipated resource needs that will have to be addressed.

#### EXTRAMURAL ISSUES

I would now like to turn to some extramural program issues. Extramural support at NIH has grown from \$107.5 million in 1986 to an estimated \$504.1 million in 1989. Many new requests for research have been issued suggesting special approaches such as studies on the molecular and cellular mechanisms that lead to bone marrow suppression in AIDS and AIDS-related complex (ARC), AIDS dementia, the toxicity of therapeutic drugs for AIDS, and the pathogenesis of intestinal dysfunction in AIDS. Similarly, the extramural program at ADAMHA has grown from \$27.0 million to \$63.7 million during the same period. In a further attempt to stimulate and accelerate AIDS research, we have initiated an expedited review process for AIDS applications. I am pleased to tell you that NIH and ADAMHA expect to make funding decisions within 6 months for most research project grant applications that arrived on February 1 and March 1.



In order to accommodate this accelerated process for the current round of reviews, additional senior staff from NIH and ADAMHA institutes have been assigned temporarily to help existing review staff identify on arrival the 200-300 AIDS applications that are anticipated. This will allow prompt assignments and referrals to appropriate initial review groups (IRGs) and awarding components, so that initial reviews will be possible in the last two weeks of April. In turn the applications' review will be expedited by the NIH Division of Research Grants' newly formed large, multidisciplinary AIDS Study Section, capable of reviewing all facets of basic and applied AIDS research. This review schedule will lead to special Advisory Council reviews by July, with awards in August. For future rounds, special receipt dates for AIDS-related applications also have been set. For now, current staff from other programs have temporarily taken on these extra duties; this difficult situation will be eased when the positions we have allocated for expediting the review are filled. We will monitor the need for additional personnel and associated resources as the volume of AIDS-related applications grows.

Extramural support for facilities renovation, expanded clinical research, and the availability of animal models for research are also being emphasized. We have just announced the Research Facilities Improvement (RFI) Program. In the FY 1988 continuing resolution, the sum of \$23.9 million was appropriated "... for repair, renovation, modernization and expansion of existing facilities, and purchase of associated equipment." The Division of Research Resources has coordinated this program closely with the NIH AIDS Executive Committee. We intend to award competitive grants in the range of \$250,000 to \$1,000,000, with no requirement for matching funds, to those institutions submitting applications judged most meritorious in the peer review process. Awards are scheduled for December 1, 1988.

Fiscal year 1988 funding of \$12.5 million will provide support for expanded AIDS and AIDS-related research to an estimated 50 of the 78 General Clinical Research Centers. These funds will support alterations and renovations, the addition of nurse FTEs, and funds for additional patient days and outpatient visits. Similar expansion of the clinical research centers mechanism for AIDS research is also a part of the ADAMHA portfolio.

We are also working to address several problems in regard to research animals, and we need to ensure proper containment to protect other animals in colonies, as well as animal caretakers and scientists. In FY 1988, the Division of Research Resources (DRR) estimates that breeding will be increased for retrovirus-free rhesus monkeys for Simian AIDS studies, but that increase will only partially allay the concern that insufficient numbers of nonhuman primates are available from either domestic or foreign sources to study prototype AIDS vaccines and therapeutic interventions. In addition, we have increasing public concern over the use of animals in laboratories and the need to provide lifetime care after studies have been completed.

The Public Health Service AIDS Animal Models Committee has just asked NIH to reserve approximately 250 chimpanzees that have been infected with hepatitis for possible future use in AIDS research. This effort will begin in FY 1988. DRR will undertake renovation of 3-5 chimpanzee holding facilities to assure that some 75 of those animals, which were inoculated with HIV under government-sponsored protocols, will be provided with adequate living quarters. Our long-range plan is to house all 250 chimpanzees that might be used in AIDS research.

## INTRAMURAL PROGRAM

We recently expanded NIH's capacity to conduct clinical research on AIDS patients through a new allocation of beds at the NIH Clinical Center for additional Phase I drug studies. The first Phase I study of an AIDS candidate vaccine in this country began in October at the NIH Clinical Center, with additional candidate vaccines moving toward testing in our network of our extramural Vaccine Evaluation Units.

The NIH intramural program is also the site of targeted programs on AIDS research sponsored by the parent institutes and by a specialized program under my Office. The latter program, instituted in 1987, was created to design new antiviral agents or improve existing ones based on new insights on the detailed fine structure of HIV protein and ribonucleic acid functions. The program, funded at about \$5 million, involves 9 institutes and over 100 investigators, and is projected to continue into 1990 and beyond. In addition, the NIMH intramural program is conducting basic and clinical research on AIDS.

In the treatment area, various drugs and combinations of drugs are being studied both at the NIH and through the AIDS Clinical Trials Group (ACTG) around the country. One of the most promising treatments being studied by the NCI is a combination of AZT and a related drug dideoxycytidine, both pioneered as AIDS therapies at the NIH. We also have just begun a trial of trimetrexate

as an experimental drug for treatment of Pneumocystis carinii pneumonia in AIDS patients who suffer serious adverse reactions to the existing approved medicines. In addition, trimetrexate will be distributed as a "treatment investigational new drug" through the National Institute of Allergy and Infectious Diseases.

#### Clinical Center

Patients with AIDS have been cared for throughout the Clinical Center for several years now, by competent staff who approach these patients with full realization of the special nature of their disease. In 1987, there were 4,487 outpatient visits for HIV-related illnesses or protocols; 205 inpatient admissions; and 118 admissions to the Medical Intensive Care Unit. The need for specialized patient counseling has been met by the work of several departments -- Nursing, Spiritual Ministry, Social Work, Hospital Epidemiology, and the Office of Bioethics. The number of patients served by these offices appear to be growing, and we will employ a counseling coordinator and set up a specific office where patients can be helped.

Fifteen examining rooms in the 11th floor clinic have been given over to the exclusive use of staff performing clinical studies of HIV-infected individuals. Physicians from NIAID and the Clinical Center are conducting Phase II drug studies as well as vaccine trials. Much of the clinical work



for these studies has been performed by specially trained clinical nurses. The clinic has been outfitted with a pioneering computer system which allows the instant transfer of laboratory data and other information from the hospital medical information system (MIS) to personal computers, where case data can be assembled and evaluated with speed and ease.

## 12 East

To initially staff 12 East, a new 26-bed unit for research on AIDS and cancer, was opened in February 1988, and an additional 38 FTEs were allocated to this unit. The medical services on the unit are to be provided by the National Cancer Institute (NCI), to which the unit is permanently assigned, but it is expected that clinical researchers from multiple institutes, e.g., the National Cancer Institute, the National Institute of Mental Health, and the National Institute of Neurological and Communicative Disorders and Stroke, will use the facility for collaborative AIDS projects. For the first phase of 12 East operations, 24 nurses will be hired to staff 14 beds.

A great deal of effort has been applied to issues involving the recruitment and retention of nurses for this and other units. A national and local nursing shortage has made compensation issues paramount in our recruitment efforts. We have recently received approval to increase the salaries of Clinical Center nurses, and our salary schedule is now in accord with our local competitors. This increase, together with new scheduling options and an aggressive advertising campaign, makes us optimistic that an ever-increasing number of beds will be ready for service.

Beyond physicians and nurses, other specialists are being brought on board for this clinical research unit. Staffing 12 East will require a full complement of allied health professionals in such fields as nuclear medicine, ultrasound evaluation, and physical therapy.

The services of allied health professionals are vital to the care of all patients at the Clinical Center -- especially those who have complex illnesses such as AIDS.

#### SPACE FOR THE CONDUCT AND MANAGEMENT OF AIDS RESEARCH PROGRAM

The two most pressing problems are the shortage of space to accommodate both researchers and program administrators, and the need to renovate laboratory facilities and/or upgrade them to ensure that all work is done at appropriate biosafety levels. The situation is becoming acute because of the increasing numbers of researchers involved in the AIDS effort, the hazardous nature of some of the research, and the additional staff needed to administer the extramural programs. Leasing of additional space and renovation of existing space, as necessary, are the quickest ways to alleviate the problem.

To address this problem, we plan to allocate \$19.15 million of FY 1988 appropriations specifically designated for AIDS-related construction, renovation, and leasing of space. Of this amount, \$10.5 million has been allocated to an addition to the A wing of the Clinical Center. This will provide office and laboratory space to NCI and NIAID for AIDS research and

office space for the Clinical Center personnel in support of AIDS research. To lease office and laboratory space for NIAID, we plan to spend \$650,000. Renovation of laboratory space in the Twinbrook-II Building to house the NIAID AIDS Vaccine Development and Treatment Center, including provision for BL-3 biosafety levels, will cost \$4 million, and \$4 million will go to a new building for NCI at the Frederick Cancer Research Facility. The most hazardous AIDS-related activity -- growing HIV-1 at high concentration -- will be housed in the new building at Frederick. This virus is now being produced in several locations, with less than optimum facility support. Other AIDS research activities will move into the space vacated by consolidating these activities.

Additional off-campus office space of approximately 16,000 square feet has been made available for AIDS-related activities, primarily contract and grant administration. Most of this (13,000 square feet) has been newly leased for this purpose. Additional office space of 25,000 square feet has been requested for leasing through the General Services Administration, in buildings already housing NIH office activities. Some problems still exist and will need to be faced in the next several years so that we can proceed with the AIDS efforts most efficiently and effectively.

In the Clinical Center, we are reviewing bed capacity requirements in the Medical Intensive Care Unit (MICU). While future intensive care needs for AIDS protocol patients will depend on specific research protocols, we would expect that over the long run we will be investigating AIDS in increasingly seriously ill patients.

## BIOSAFETY CONCERNS

Following the recent infection with HIV of two AIDS laboratory workers in contract laboratories, it became increasingly clear that adequate precautions and steps must be taken to ensure the lowest risk possible to such workers. This issue has been addressed both by the NIH Division of Safety (even before the first sero-positive worker was proven to have been infected in the laboratory) and by a panel of NIH biosafety officials and experts from the academic community. The conclusions of this expert panel were that current biosafety guidelines are adequate.

To be certain that compliance with the guidelines is optimal, the NIH Division of Safety has increased efforts to ensure that all laboratories working with HIV are communicating regularly with this office, and that procedures are established for continued monitoring of biosafety by the responsible laboratory supervisor.

However, overcrowding and inadequacy of laboratory facilities from a biosafety perspective are real and continuing problems. Laboratory space that was designed and built 30 years ago, to serve fewer than half of the current occupants, needs to be reexamined. There is a definite need to upgrade current laboratories with appropriate hoods, to provide containments to prevent dispersion of aerosols from centrifuge experiments, and to construct BL-3 facilities for certain critical operations. Current AIDS construction funding is being used to address these problems.



#### FTE LEVELS FOR THE EXPANDED AIDS EFFORT

The staffing problems faced by the Clinical Center are mirrored in the management of our overall program. As a result of the substantial expansion and establishment of new AIDS research activities, there is also a need to provide additional staff to extramural program management to ensure that the AIDS efforts are carried out in an effective and efficient manner. Some of the research areas requiring additional personnel for expanded activities are: development, coordination and monitoring of clinical trial protocols; administration and monitoring of contracts and grants; and maintenance of high quality and expeditious peer review of grant applications and contract proposals. These requirements are being addressed with increased staffing for AIDS in Fiscal Years 1988 and 1989.

Despite recent provision of additional FTEs for AIDS activities, we expect to have difficulty recruiting and retaining personnel to support these expanded efforts. Salaries for senior level researchers and physicians are generally not competitive with those earned by their counterparts in non-Federal settings. As noted above, these and other related issues also will be addressed as part of the independent IOM evaluation planned to begin this spring. The recent doubling of maximum physicians comparability allowances also will help address the concern.

## COMMUNICATIONS

NIH has sponsored a number of major conferences relating to AIDS -- most notably, NIH organized the III<sup>rd</sup> International Conference on AIDS held in July 1987 in Washington, D.C. In addition, NIH scientists working on AIDS have attended scientific meetings since the beginning of the epidemic to encourage other scientists to apply their expertise to the problem of AIDS and to forge collaborations with other institutions and researchers.

To enhance information exchange, the National Library of Medicine (NLM) will soon develop improved computerized information services to be used by researchers everywhere. The new services will make up-to-the-minute research findings emanating from NIH, university and industry laboratories available to scientists. This new service will be in addition to the quarterly publication of AIDS Bibliography, begun by the NLM in January 1988.

To help communicate important information on AIDS to practicing physicians and health care professionals -- many of whom are just beginning to encounter patients with AIDS -- NIH has a number of ongoing projects. NIAID has organized about two dozen workshops for allied health professionals in cities across the country and in Puerto Rico. The conferences present information on the epidemiology of AIDS, patient management, and ethical, legal, and psychosocial issues of concern to those who care for persons with AIDS. The National Institute for Dental Research has developed an outreach program aimed at dentists and other dental health professionals to inform them of safety considerations in the practice of dentistry. The National Heart, Lung, and

Blood Institute has begun the National Blood Resources Education Program, a major effort to promote an adequate and safe supply of blood and to enhance the proper utilization of blood and blood components.

Mr. Chairman, this concludes my prepared statement, but I will be pleased to respond to any questions you or members of the Committee may wish to ask.

REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

- O I am pleased to have this opportunity to report to you on several matters that are important to the National Institutes of Health at this time, and most of them, I believe, will be of interest to you.

THE PRESIDENT'S FY 1989 BUDGET REQUEST FOR NIH

- O The total request for all NIH programs, including the recommended support for AIDS research, is for \$7.123 billion, an increase of 6.8 percent over 1988. Within the budget request an amount of \$587.6 million is proposed for AIDS research. This is an increase of 26 percent over the allocation for AIDS in FY 1988. For all NIH programs other than AIDS the increase is 5.4 percent.

The request would support a total of 21,145 project grants, almost 1000 more grants than we are supporting during the current year, and more than twice the total of 10,175 project grants we funded in 1970.

A total of 5,761 new and competing renewal grants could be made under the proposed budget. This is 291 fewer than we expect to make during the current fiscal year.

- O The President's request would allow average cost increases for research project grants of about 4.7 percent for noncompeting awards and 2.9 percent for competing awards.

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\*Presented at the Association of Academic Health Centers  
spring meeting, Washington, D. C., March 26, 1988.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



The average awards, however, would be 10 to 13 percent below the estimated full cost levels for competing and noncompeting awards respectively. This increasing divergence between the actual costs of research projects and NIH awards for their support leads to an escalating amount of "cost sharing" by grantee institutions.

- O What we are seeing is in part a result of our efforts to "stabilize" the opportunities for investigators by establishing a target number of new and competing renewal grants. For a time this preferential treatment of grants could be accommodated within the overall budget by reducing our allocations to other mechanisms of research support, but there is a limit beyond which this shifting of funds is no longer feasible. We are now in the situation where the necessity for funding target numbers of grants within fixed amounts of funding predetermines the amount of the average grant. In order to make the required number of grants, we have no choice but to reduce individual awards by considerable amounts below the full cost as estimated by the grantee institution and after peer review.
- O The amount of the average noncompeting grant under the FY 1989 request will be \$191,000, and the average for new and competing renewal project grants will be \$181,000.

If inflation is taken into account the total amount of the average project grant has remained essentially constant over the past 20 years. However, there has been a steady decline in the share of funds available for the actual conduct of research because the portion of the average award required for indirect costs has increased from 24 percent in 1974 to 31.3 percent in 1987.

- O The FY 1989 request for research centers, \$539.2 million, would provide support for 555 centers, three fewer than under the current budget. General clinical research centers would receive a 2 percent increase. Average costs for all other center grants would be approximately the same as the FY 1988 level.

- O Research training and career development activities would remain close to their FY 1988 operating levels with an increase of 3 percent for research career programs and a 2 percent increase for research training.
- O The NIH intramural research program would receive \$670.6 million, an increase of 3.7 percent over the FY 1988 comparable level. The additional funds would be used to support built-in increases.

#### THE "PRIVATIZATION" OF NIH

- O In what the White House press office later called a "trial balloon," the OMB proposed that consideration be given to various changes in the status and organization of intramural NIH, including the possibility making it a non-Federal university or research institute. This proposal has been greeted with practically unanimous dismay and disapproval in both the scientific and academic communities. And there seems to be a considerable amount of opposition to the idea in the Congress.
- O I have expressed my opposition to the proposal as a potentially destructive remedy for problems that could be solved by much less drastic measures. At the same time I am encouraged that the Office of Management and Budget has taken note of some of the problems we face, particularly the erosion in our ability to retain leading investigators because of the widening gap in the salaries and other benefits available to our senior scientists, together with the inhibiting effects of Federal administrative requirements as compared with those applying to their counterparts in the academic community.
- O The OMB has asked the Department of Health and Human Services and the NIH to consider a wide range of strategies for assuring the continued scientific excellence of the intramural program, and suggested that we ask the Institute of Medicine to undertake a study of the options and make a preliminary report at least by June 1.

## MAPPING AND SEQUENCING THE HUMAN GENOME

- O An amount of \$17.5 million was earmarked in the FY 1988 appropriation for the genome mapping project, and an additional \$3.8 million was included for the establishment of a related biotechnology information center at the National Library of Medicine. The President's request for FY 1989 includes \$28 million for the mapping and \$4 million for the information center. Thus, the Congress, through the 1988 appropriation, and the Administration, through the President's 1989 budget request, have sent a clear message that this is an important program, that there are immediate and long-range implications for public health, and that mapping the human genome should begin at once.
- O An expert committee of the National Academy of Sciences has urged an immediate beginning of a program to discover the location of every gene within human chromosomes. In a statement accompanying their report, the Academy's committee stated its confidence that "Such a special effort in the next two decades will greatly enhance progress in human biology and medicine." They also emphasized the need to study the genetic make-up of other animal species to provide comparative data.
- O On February 29, this year, we assembled an ad hoc program advisory committee of some of the nation's outstanding leaders in the biosciences to discuss, in some detail, priorities and principles to be applied in carrying out a major NIH program for mapping and sequencing the human genome. The ad hoc committee unanimously endorsed our plan to establish an Office of Research on the Human Genome, headed by a new Associate Director, within the Office of the Director, NIH. The office will have responsibility for development of new proposals as well. We will charter an NIH Program Advisory Committee on the Human Genome. We intend to tap the best minds in the related disciplines in order to develop scientific plans and administrative options for promoting rapid progress in methods of mapping and sequencing, and for managing the wealth of information emanating from these studies.

- With the enactment of the FY 1988 appropriation and the President's budget request, we feel confident that we can proceed with the highly important human genome project without risking the possibility that it would become a competitor and siphon funding from our other vital programs.

#### A CONTINUING SUPPLY OF SCIENTISTS

- Continued availability of a supply of high quality scientists is essential to the nurture of the biomedical research enterprise. It is our special responsibility as scientists, academicians, and administrators to help assure the future supply of trained scientists. We have totally new disciplines within the biosciences so that larger numbers of more highly trained investigators will be needed if we are to continue successfully the pursuit of discovery in new areas, such as structural biology and molecular genetics.
- The Government-University-Industry Research Roundtable, of the National Academy of Sciences, has been holding thoroughgoing discussions of the issues relating to the development, identification, recruitment and retention of science and engineering talent. In evaluating the talent pool, they predict that the demand for scientists and engineers will remain strong in both industry and academia, but that at the same time the number of Americans qualified for these careers may be declining.
  - The supply of 22-year-olds is projected to drop more than 25 percent before the end of the century.
  - If even the current level of supply for industry and academia is to be maintained, a significant increase in the proportion of 22-year-olds attaining scientific and engineering degrees will be necessary. The Roundtable group estimated that to maintain the 1985 level into the 1990s, the degree award rate would have to increase by 30 percent.
  - A substantial drop in the number of baccalaureate degrees in the life sciences that began in the late 1970s continues unabated.



The number of women and minorities graduates is on the increase but their numbers do not make up for the losses.

- O There has been a persistent decline in the number of younger applicants for traditional NIH grants. More than 26 percent of all applicants were under 36 years of age in 1979, but seven years later less than 14 percent were under 36.
- O On the average, NIH-supported investigators are older today than in previous years. The average age in 1979 was 41.9 years, and in 1985 it was a full year older--42.9 years.

#### REPORT OF STUDY GROUP ON EXTRAMURAL BIOMEDICAL RESEARCH FACILITIES CONSTRUCTION

- O The Senate Committee on Appropriations last year directed the NIH to address the issue of biomedical research facility construction on the ground that "research is hampered by aging and obsolete research facilities and instrumentation." In response we brought together an ad hoc study group made up of key leaders from universities, academic medical centers, and nonprofit research institutions. Dr. David Challoner, Vice President for Health Affairs of the University of Florida, was a member of the group that was chaired by Dr. Steven Beering, President of Purdue.
- O The study group met February 9-10, received testimony from individuals representing a variety of organizations and institutions, and made recommendations that we have transmitted to the Committee on Appropriations.
- O The group cited their finding that an overwhelming need currently exists as the basis for recommending a long-term research facilities program.
- O The group recommended that the Federal Government assume a strong leadership position in addressing the nation's biomedical research facilities needs---that the NIH be given an overall construction

authority in addition to existing Institute authorities--and that selection criteria should be based on scientific merit as established through the traditional NIH peer review process.

- O In addressing the financing of facilities, the Group cautioned that new Federal monies should be allocated for construction, so that such support not be at the expense of research and training programs. They further recommended that:
  - o There be a 50/50 matching requirement for construction grants.
  - o The indirect cost use allowance be raised and separate indirect cost for capital and operating expenses should be allowed.
  - o The Federal Government should consider establishing a construction loan guarantee program for biomedical research facilities, and possible changes in the Tax Reform Act to encourage philanthropy and restore tax incentives for facilities construction.
- O The Study Group further recommended a 10-year NIH Research Facilities Construction Program, including a 2-year pilot phase. They suggested:
  - o An initial commitment of \$100 million in year 1 and \$200 million in year 2 to help shape and refine the objectives and administration of the longer term effort. New building construction and major expansion of facilities would not be included in the pilot phase. These needs would be addressed beginning in year 3.
  - o Years 3 through 10 should be funded at levels from \$350 million to \$500 million, with individual awards restricted to a minimum of \$ 250,000, with not more than 5 percent of the total appropriation in a year to go to any one institution.
  - o That awards be based on the traditional two-tier NIH peer review system taking into account the general objectives of the construction program.

RESEARCH ON AIDS

- O To assist in setting research priorities for AIDS research at NIH, I recently established an AIDS Program Advisory Committee with membership drawn from the country's most distinguished scientists, administrators and ethicists. A new Associate Director for AIDS Research will be appointed who will report to the NIH Director.
- O A plan to speed up the review and award of grants for AIDS research is being announced to the extramural community.
- O Intramurally we recently expanded NIH's capacity to conduct clinical research on AIDS patients through a new allocation of beds at the NIH Clinical Center for additional Phase I drug studies. Our intramural and extramural efforts in the areas of drug and vaccine development continue. The first Phase I study of an AIDS candidate vaccine in this country began in October at the NIH Clinical Center, with additional vaccines moving toward testing in our network of Vaccine Evaluation Units.
- O The President's FY 1989 funding request proposes consolidation of funding for AIDS in the Office of the Assistant Secretary for Health.

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STATEMENT

BY

JAMES B. WYNGAARDEN, M.D.

DIRECTOR

NATIONAL INSTITUTES OF HEALTH

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON LABOR AND HUMAN RESOURCES

U.S. SENATE

MARCH 29, 1988



Madam Chairwoman and Members of the Committee:

I am pleased to have the opportunity to discuss the reauthorization of expiring programs of the National Institutes of Health, the status of biomedical research facilities, and the issue of pay and retention of senior scientists at NIH.

NIH authorities expiring at the end of fiscal year 1988 include programs of the National Library of Medicine, the National Research Service Awards Program, the advisory boards of the National Institute of Diabetes and Digestive and Kidney Diseases, and programs of the National Cancer Institute, and the National Heart, Lung, and Blood Institute.

#### NATIONAL RESEARCH SERVICE AWARDS

Since the inception of NIH, the interdependence of research training and research has been recognized. This linkage provides an opportunity for new discovery and development of the next generation of scientists to occur in the same laboratories. The National Research Service Award (NRSA) programs serve several functions: they provide an opportunity for students to pursue research careers, they enhance research environments, and most of all, they support the Nation's research enterprise by ensuring the flow of well-trained young scientists into research careers. Between 10,000 and 11,000 NRSA positions are supported by NIH each year, with approximately equal numbers of pre- and

postdoctoral positions. Most predoctoral positions are Ph.D. traineeships. More than half the postdoctoral traineeships support M.D.'s. In addition, NRSAs are supported by the Alcohol, Drug Abuse, and Mental Health Administration and by the Health Resources and Services Administration.

Section 487(d)(3) of the Public Health Service Act requires that half of one percent of NRSA funds be made available for research training in primary care. In FY 1988, NIH will award more than one-half percent of NRSA funds for institutional training grants related to primary care research training in the areas of pediatrics, family practice, internal medicine, dentistry, and mental health. These funds will be awarded to grant applications received in response to our direct solicitation to increase efforts in this area.

With the dynamic expansion and sophistication of biomedical research, there continues to be a need to provide adequately trained manpower to answer the important research questions. At the same time, with the number of graduates in total declining, commensurate falling enrollments in fields of study related to biomedical science and pressures to pursue lucrative non-research careers challenge us to assure a steady flow of manpower into biomedical research. The number of employed biomedical scientists has been increasing--412,000 life scientists were working in 1986, up from 353,000 in 1984 and 214,000 in 1976. Continued support of NRSA awards, as proposed in the President's FY 1989 budget, would add more biomedical researchers to this pool.

## MEDICAL LIBRARY ASSISTANCE ACT

Effective biomedical information services are essential if we are to attain the maximum benefits from our investment in research and treatment of major human afflictions. The programs authorized by the Medical Library Assistance Act (MLAA) and administered by the National Library of Medicine form the foundation for much of the work in providing this assurance. Since passage of the MLAA in 1965, NLM has assisted health science libraries throughout the country to establish, expand, or improve their information services.

Although results have been impressive, continued growth in the biomedical literature and the increasingly interdisciplinary nature of scientific research require that health professionals have access to a very wide range of information from many different sources. An even stronger, more technically advanced communications network to provide effective access to all that information is essential. Our nation's medical libraries must have available the latest information technologies, equipment, and services to aid health care professionals. The NLM's library assistance programs help provide the means, and represent the only direct Federal assistance programs focused on this effort. The President's FY 1989 budget seeks \$ 9.790 million for this program, up from \$ 9.414 million in FY 1988. In total, the President's FY 1989 budget seeks a 4-percent increase for the NLM, up from \$67.9 million in FY 1988 to \$70.6 million in FY 1989.

Biotechnology, as a new field, has special requirements for information handling. To reap the potential benefits of research in this field and

harness the biotechnology information that is being generated by the nation's laboratories, the National Library of Medicine will spend \$3.8 million in FY 1988 on the National Center for Biotechnology Information, which will coordinate and integrate the form and content of the databases in this area and provide for distribution of biotechnology data via electronic means. An additional \$4 million is proposed for FY 1989. The work of this Center will be crucial in the forthcoming research on sequencing and mapping the human genome.

#### OTHER EXPIRING AUTHORITIES

Three other NIH authorities are expiring at the end of the fiscal year: the mandate for National Advisory Boards of the National Institute of Diabetes and Digestive and Kidney Diseases and the authorizations of appropriations for the National Heart, Lung, and Blood Institute and the National Cancer Institute. The NIDDK boards serve an important long-range planning function, provide a framework for interagency dialogue and cooperation, and serve as an expert source of advice for NIH and the Department. The NHLBI combines a balance of basic, clinical, and applied research; research training; and demonstration and education activities that have contributed to the health and well-being of the nation. The NCI continues its commitment to the support of basic research, which is the basis of the Institute's treatment research and prevention studies involving dietary and lifestyle changes. The Administration is developing legislation related to NIH's expiring authorities.

Madam Chairwoman, we are concerned with the proliferation of institute-level components within the NIH. In 1984, the Institute of Medicine (IOM) issued a



report dealing with the organizational structure of the National Institutes of Health. The IOM committee found the evidence about the desirability of organizational change at NIH to be mixed, in part because such changes may add significant administrative costs without ensuring increased resources for the research effort. In viewing NIH's organizational development, the IOM concluded that "NIH has reached a point at which there should be a presumption -- to be overridden only in exceptional circumstances -- against additions at the institute level." As an alternative, the IOM recommended that NIH "should avail itself of a range of activities, short of establishing new institutes, to respond to health needs and opportunities."

In these times of fiscal restraint, it is more productive to focus our attention on expanding the broad base of existing research. Monies that would be needed for startup and continued administrative costs for large new units could be more efficiently used in support of research. The Department of Health and Human Services believes the creation of additional NIH institutes and centers should be viewed with caution.

Beyond our expiring authorities, we understand that the Committee wishes us to address biomedical research facilities and senior staff recruitment and retention.

#### BIOMEDICAL RESEARCH FACILITIES

There have been many expressions of concern both to the Congress and NIH regarding the substantial need for new biomedical research facilities and for

repair and renovation of deteriorating facilities. There have been major advances in the volume and quality of the scientific knowledge base, and new technologies and scientific opportunities are developing rapidly. Special requirements for protection of research workers and the public from biological and chemical hazards and increased security needs have placed greater demands on our existing facilities. There are continual needs for alteration and renovation of laboratory animal facilities, as well as an inevitable backlog of repairs and remodeling of aging and deteriorating facilities. Some facilities should not be repaired or renovated, but completely replaced.

We are studying the adequacy of existing research facilities, as well as the extent of need for renovation and improvement of inadequate facilities by our universities. As you know, Federal agencies expend several hundred million dollars annually for university research facilities through overhead charges. The National Science Foundation (NSF) and NIH have surveyed university administrators on the condition of research facilities. NSF data published in Science and Engineering Research Facilities at Doctorate-Granting Institutions (Sept. 1986) indicated that universities have planned or begun substantial construction and renovation projects. NSF is collecting additional data on existing and planned university facilities, to be published in the fall of 1988.

Consideration of Federal support for construction of biomedical research facilities was requested by the House and Senate Appropriations Committees in their reports on the FY 1988 budget (S.Rept.No. 100-189; H.Rept. 3058). NIH was asked to "convene a group of consultants to make recommendations on the

design, balance, and administration of a pilot research facilities program to assist universities and nonprofit research institutions in replacing obsolescent biomedical research facilities and equipment." On February 9-10, 1988, an ad hoc study group of leaders of colleges, universities, and nonprofit research institutions was assembled by NIH to address issues related to research facilities construction. We are preparing a report on the recommendations of the study group.

#### SENIOR LEVEL RECRUITMENT AND RETENTION

Concerns have been raised about recruitment and retention of researchers on the NIH campus. Recruitment and retention problems as well as limitations on the number of senior level positions have resulted in critical vacancies and deferred recruitment. A great many highly motivated senior staff have elected to remain at NIH, but recruiters from academia and industry make highly attractive offers that at best are unsettling, and only too often are accepted. While the Senior Executive Service (SES) allows NIH to promote some of our most accomplished scientists and administrators into the senior ranks, we have had limited success in attracting top caliber candidates from outside the Government. Academic institutions, industry, and independent research laboratories offer substantial salary increases. Compensation of physicians and other doctorates in academic institutions is considerably higher than that available at NIH. In the academic sector, on the average, the compensation of senior physicians is 62 percent higher than that received by NIH senior physicians, while the base pay of senior Ph.D. staff is 23 percent higher than that received by NIH senior Ph.D. staff.

At the same time, the NIH offers advantages that for many researchers offset the salary differentials. Among these are the intellectual stimulation and prestige of being a part of NIH, as well as the scientific freedom to choose their own research pursuits. Scientists at NIH have access to state-of-the-art equipment, freedom from administrative and teaching responsibilities, and opportunity for rewarding associations with outstanding scientists from many disciplines. Also, there are opportunities for consulting, although these are subject to some limitations.

Employment in the academic sector provides the prospect of superior salary supplements, fringe benefits such as tuition subsidies, and better opportunities to supplement income through private practice and consultation. In addition, the fact that there is no limit upon university salaries supported through NIH extramural mechanisms further fuels the pay competition from the academic sector.

Recent advances in the biomedical sciences and biotechnology have opened many potentially valuable and lucrative commercial applications and have caused a dramatic increase in competition for top caliber researchers and science managers in the private and academic sectors. The emergence of the biotechnology industry has contributed to the competition between senior NIH staff and their counterparts in industry and universities.

Recruitment and retention of intramural scientists should be viewed in the context of training. As a training ground for post-doctoral researchers, the intramural laboratories of NIH have helped staff the Nation's research



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universities. Many junior scientists complete their training at NIH and continue their research careers in the universities. A high percentage of this country's leading researchers are NIH alumni.

If NIH is to remain the international leader in the biomedical sciences, new approaches must be found to make our senior level personnel systems competitive with the private and academic sectors. We have asked the Institute of Medicine to study the structure and organization of NIH intramural research including recruitment and retention difficulties; their causes and effects on NIH research quality; and potential strategies to address them if warranted. We would like to study the IOM findings and recommendations before we make final recommendations on recruitment and retention issues. Further, we are in the process of implementing the provisions of Public Law 100-140, which extended and doubled the maximum PCA allowance.

Madam Chairwoman, that concludes my prepared statement. I would be pleased to answer any questions you may have.

**REMARKS\***

by

James B. Wyngaarden, M.D.\*\*

It is a pleasure to be back home this evening for the "Thank You, Grand Rapids" ceremony. As the Director of the National Institutes of Health, I am very aware of the impact of this project on the oral health of the world. In fact, I believe that water fluoridation will go down in history as one of the greatest public health accomplishments of our time.

I would like to say that I am proud of Grand Rapids for having the resolve to be the first community to fluoridate its water supply. This is a truly great city--and I am glad to call it my hometown. I share the sentiments of Dr. Littleton and all the others in wishing Mayor Helmholdt and the citizens of Grand Rapids a successful 150th anniversary year.

Last year at the NIH, we reached a milestone of our own--our Centennial anniversary. All year long we took note of the progress that has been made, particularly in the last decades, as what we recognize as a revolution in biology. That revolution has amassed a spectacular store of knowledge, and has forged the academia-private sector-government partnership in research.

The National Institute of Dental Research itself has a strong record of research excellence. Its story is a chronicle of scientific advances profoundly affecting the practice of dentistry here in the United States, and throughout the world. Research on caries, periodontal disease, developmental anomalies, acute and chronic pain, restorative materials are just a few of the many areas greatly influenced by NIDR during its 40 years.

I thank one and all for inviting me here this evening. And, I look forward to enjoying a tribute ceremony for a well-deserving city.

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\*For Celebration Honoring the Citizens of Grand Rapids for the Pioneer U.S. Water Fluoridation Project in Grand Rapids, Michigan, on April 21, 1988.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director

Mr. Chairman, it once again is my privilege to appear before you and the members of the Subcommittee to present the President's budget proposal for the National Institutes of Health. Today I will report briefly on some of our activities and plans, and describe the highlights of the request for Fiscal Year 1989. In later statements the Directors of the constituent units of the NIH will present more details about our plans and programs.

It is always a pleasure for us to appear at these hearings because of the depth of information and constructive concern that you, Mr. Chairman, the members of the Subcommittee, and the staff have consistently shown in the programs of the National Institutes of Health. Because of the Subcommittee's interest in the NIH 100th anniversary, I am happy to report the completion of the year's full and varied schedule of centennial observances. It was our objective for the centennial observance that it would help create a better public understanding of the importance of biomedical research. Further, we expected that through the events we might attract the attention of young persons in such a way as to induce them to consider the value and satisfactions of a career in biomedical research. Without going into further detail about the centennial, I am pleased to report that the observance was an unqualified success.

Recently our principal program officials and members of our major advisory groups have been holding hearings in different parts of the nation on "The Health of Biomedical Research Institutions." The meetings have been held in San Francisco, Los Angeles, New York, Boston, Dallas, Atlanta and Chicago. The sessions are attended by members of the scientific community, university officials and other interested parties, whose advice we seek concerning current and emerging NIH policies and practices and any other issues affecting the status of the nation's biomedical research institutions. We consider our working relationships with extramural institutions to be of key importance because the productivity of the nation's medical research enterprise depends in large measure upon the health of the nation's biomedical research institutions.

I am pleased to report two appointments to major NIH positions during the past year. Dr. Katherine Bick had been named our Deputy Director for Extramural Research. Following a successful career in academia, she has served with distinction for 12 years as a scientist-administrator at NIH. The other appointment was that of the first Director of the National Center for Nursing Research, Dr. Ada Sue Hinshaw. She came to NIH from the administration and the faculty of the University of Arizona's Health Sciences Center.

Among the research developments of the past year, I wish to call your attention to one in particular. It was the discovery by Dr. Michael Zasloff, of the National Institute of Child Health and Human Development, of naturally occurring substances that operate as



a chemical defense system against microorganisms. While conducting research on an entirely different subject, he made a shrewd observation that surgical wounds on laboratory frogs heal infection-free even when the frog's environment teems with infectious organisms. This led to the discovery of "magainins"--naturally occurring chemicals that protect frogs and possibly humans against infections. Our pleasure in referring to this exciting development is moderated by the fact that Dr. Zasloff will be leaving the NIH intramural programs to join the faculty of the University of Pennsylvania. While many factors usually contribute to such decisions, our ability to retain leading investigators is seriously compromised by the widening gap in the salaries and other benefits available to our senior scientists, as compared with their counterparts in the academic community, and by various Federal administrative requirements.

The Office of Management and Budget has taken note of the Federal administrative controls and procedures, including personnel procedures, space allocation procedures, congressional requirements, and the widening salary gap, that limit the capacity of the NIH intramural research program to sustain its distinguished record of scientific achievement and excellence. If the extraordinary accomplishments of the NIH intramural laboratories are to be assured over the long term, solutions must be found to these administrative barriers.

The Department of Health and Human Services has been encouraged by the Office of Management and Budget to consider a wide range of strategies for assuring the continued scientific excellence of the intramural program, and was advised to ask the Institute of Medicine of the National Academy of Sciences to undertake a study of the options. The study has been commissioned and we expect to have recommendations from the six-month study this fall.

Throughout the scientific community new techniques in the manipulation of DNA and the development of new methods of automated processing of DNA are yielding large volumes of information regarding the human genome. Characterizing the entire human genome will have profound implications for understanding the more than 3500 diseases that are known to involve a genetic defect. This knowledge will enhance our understanding of the normal processes of development by many fold.

Every day brings new information on the location of genes. The locations of new markers, particularly those in close proximity to genes associated with known genetic disorders, are published in each issue of the leading scientific journals. Information on the location of individual genes will become known through the course of scientific inquiry, but if we are ultimately to succeed with this project we must capture information systematically for the construction of the complete map. The staggering volume of molecular data and its cryptic and subtle patterns have led to an absolute requirement for computerized data bases and analytical tools if we are to succeed in this major advance.

In the NIH appropriation for FY 1988 an amount of \$17.3 million was earmarked for the genome mapping project, plus an additional \$3.8 million for the establishment of a related biotechnical informa-

tion center at the National Library of Medicine. The President's request for FY 1989 includes \$28 million for the mapping and \$4 million for the information center. Through the 1988 appropriation and the FY 1989 President's budget, both the Congress and the Administration have sent a clear message that this is an important mission, and that there are immediate and long range implications for public health, and that mapping the genome should begin at once.

An expert committee of the National Academy of Sciences has urged an immediate beginning of a program to discover the location of every gene within human chromosomes, noting that such an effort within the next two decades would greatly enhance progress in gaining new knowledge of human biology and medicine.

While the report was controversial in some aspects, it is sound conceptually. Our 1988 and 1989 efforts signal the beginning of this effort. To coordinate this effort I plan to establish an Office of Research on the Human Genome, headed by an Associate Director within the Office of the Director of NIH. The new office will have a coordination and integration function with regard to our ongoing efforts within all components of NIH. We look forward to the establishment of an NIH Program Advisory Committee on the Human Genome, and for it we intend to tap the best minds in the related disciplines in order to develop a scientific plan and administrative options for promoting rapid progress in methods of mapping and sequencing, and for managing the wealth of information emanating from these studies.

Permit me to mention a few highlights from recent research activities.

- o A major study supported by the National Institute of Child Health and Human Development has concluded that the drug cysteamine can prevent kidney failure and permit normal growth when given to very young children who inherit the rare metabolic disease cystinosis. This represents the first effective therapy for any of the genetic disorders known as lysosomal disorders.
- o Earlier this year a prevention study, supported by the National Heart, Lung, and Blood Institute, showed that one aspirin tablet taken every other day significantly reduces the incidence of fatal and non-fatal heart attacks in men who had no history of heart attacks.
- o Advances made by intramural scientists from the National Institute of Allergy and Infectious Diseases are rapidly moving us toward the development of a vaccine against rotaviruses, the most important cause of severe diarrhea--sometimes leading to death--among young children.
- o Scientists supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases have recently discovered that an immunosuppressive drug, cyclosporin A, is highly effective in the treatment of psoriasis, a chronic skin disorder. This discovery--in addition to the evidence showing that a high percentage of HIV-positive patients have symptoms of psoriasis--



redirects scientists to look more closely at the possibility that psoriasis is an immune disorder.

- o During the past year, studies supported by the National Cancer Institute developed the first highly effective regimen for advanced bladder cancer, a cancer that affects nearly 50,000 Americans each year. In a study of combined chemotherapy using four drugs, there was an overall response rate of 70 percent in advanced bladder cancer, with 37 percent of patients having complete remission.

The NIH has a major research commitment in AIDS. Sixteen NIH components, stressing research in pathogenesis, therapeutics, and vaccine development, are involved. To assist in setting research priorities for AIDS research at NIH, I recently established an AIDS Program Advisory Committee with membership drawn from the country's most distinguished scientists, administrators and ethicists. Another new development in AIDS is our program to speed the review and award of AIDS grant applications. The plan will be announced to the scientific community shortly.

Intramurally, we recently expanded NIH's capacity to conduct clinical research on AIDS patients through a new allocation of beds at the NIH Clinical Center for additional Phase I drug studies. Our intramural and extramural efforts in the areas of drug and vaccine development continue. The first Phase I study of an AIDS candidate vaccine in this country began in October at the NIH Clinical Center, with additional candidate vaccines moving toward testing in our network of Vaccine Evaluation Units.

In the treatment area, various drugs and combinations of drugs are being studied both at the NIH and through the AIDS Clinical Trials Group (ACTG) around the country. One of the most promising treatments being studied is a combination of AZT and a related drug dideoxycytidine, both pioneered as AIDS therapies at the NIH. We also are making use of trimetrexate as an experimental drug for treatment of pneumocystis carinii pneumonia patients who suffer serious adverse reactions to the standard therapy. For this purpose trimetrexate is being distributed under a new FDA procedure as a "treatment investigational new drug" through the National Institute of Allergy and Infectious Diseases. In addition, we have just begun a clinical trial to compare the results from treatment with trimetrexate with the effects of treatment with other drugs. NIH's program to apply techniques of structural biology to the design of new drugs for the treatment of AIDS has begun.

The FY 1989 funding request proposes consolidation of funds for AIDS in the Office of the Assistant Secretary for Health. The amount identified for NIH is \$587.6 million, an increase of \$119.8 million or 26 percent over the FY 1988 estimate. Detailed descriptions of the AIDS research conducted and supported by the various NIH components are contained within the individual budget justifications and in the PHS consolidated submission.

Mr. Chairman, the FY 1989 budget request for the National Institutes of Health is \$6,535.2 million, an increase of 5.4 percent over the comparable FY 1988 level of \$6,198.9 million. For

comparability with FY 1989, funding for acquired immunodeficiency syndrome (AIDS) is excluded from the FY 1988 total.

The FY 1989 request will support a total of 20,600 research project grants, the largest total number of research grants ever awarded by NIH, 837 more awards than the FY 1988 comparable level. The total number of research project grants, excluding AIDS, is made up of 14,989 noncompeting continuations and 5,611 new and competing renewal awards.

The President's request would allow average cost increases for research project grants of about 4.7 percent for noncompeting awards and 2.9 percent for competing awards.

The FY 1989 request for research centers, \$539.2 million, would provide support for 555 centers, three fewer than under the current budget. General clinical research centers would receive a two percent increase. Average costs for all other center grants would be approximately the same as the FY 1988 level.

Research training and career development activities would remain close to their FY 1988 operating levels with an increase of 3 percent for research career programs and a 2 percent increase for research training.

The NIH intramural research program would receive \$670.6 million, an increase of 3.7 percent over the FY 1988 comparable level. The additional funds would be used to support built-in increases.

Mr. Chairman, this completes my opening statement, but I will be pleased to respond to any questions you or members of the committee may wish to ask.





STATEMENT BY  
JAMES B. WYNGAARDEN, M.D.  
DIRECTOR  
NATIONAL INSTITUTES OF HEALTH  
PUBLIC HEALTH SERVICE  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
BEFORE THE  
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS  
HOUSE COMMITTEE ON ENERGY AND COMMERCE  
April 27, 1988

Mr. Chairman, Members of the Subcommittee:

I would like first to commend you for recognizing the potential significance of the human genome initiative at a very early stage in its development. As a result of your initial request two years ago, today we have a comprehensive and timely assessment of the policy issues concerning mapping the human genome. I am pleased to have the opportunity to describe the plans NIH is developing for our participation in this important area of human biology.

#### Rationale for the Human Genome Initiative

Genetics, the science of inheritance, has been a primary research area of the NIH for the last several decades. As you heard from the previous speakers, we are currently in the midst of an explosion of biological knowledge. This greatly accelerated pace of discovery really started when the genetic material called deoxyribonucleic acid (DNA) was found, in 1953, to have a double-stranded twisted structure called a double helix in which opposite strands were precisely joined. Built into this structure was the mechanism for passage of genetic information from one generation to the next. For this discovery, Dr. James Watson, along with his British colleague, Dr. Francis Crick, were awarded the Nobel Prize.

Since then, discovery after discovery in the area of genetics have come so rapidly that the term "biological revolution" is often used. Almost all these new findings have come from American scientists supported by NIH. Six additional Nobel Prizes have been awarded to scientists for work on DNA structure--all of whom received substantial support from NIH. The Congress of the United States has recognized the importance of such research to the well-being and improved health of the American people and has consistently supported the NIH budget for this work.

The current budget for NIH is \$6.7 billion, of which about \$2.4 billion is in an area called biotechnology. About one-half of this amount, or \$1 billion, is devoted to genetics, DNA research, and the related science base. This field has developed rapidly, as a result of the discovery of a technique known as recombinant DNA technology which permits the snipping of a small piece of DNA from one site in the gene, and its insertion into another--even into the DNA of another different organism, if that is desired. Again, this discovery was made by American scientists who also won the Nobel Prize. The use of this technology has not only spawned the new biotechnology industry, which is able to produce important chemicals and drugs, but has also made it possible to map and eventually to sequence the entire human genome, the complete genetic material of man. The latter project is actually feasible now, and with further methodological advances will be done more easily and less expensively in the future.



Characterizing the genomes of a number of complex organisms is a natural outgrowth of all our efforts directed toward understanding biology. NIH has long been committed to the support of research leading to a full understanding of the genetics of normal human development and of what goes wrong in human disorders. This work is absolutely indispensable to the mission of the NIH, which is to acquire a deep understanding of how biological systems develop and function, and what goes awry in the thousands of diseases that affect mankind. In fact, molecular biology and molecular chemistry constitute the basis for all of modern biomedical research.

In Fiscal Year 1987, NIH provided over \$365 million of its funds to about 3,000 research projects related to the elucidation of complex genomes, of which about \$110.5 million was related to mapping and sequencing the human genome. Scientists supported by NIH are now engaged in many projects to "map" or pinpoint the specific location of genes on chromosomes, especially those genes responsible for inherited disorders. Researchers have already mapped many genes and have found the approximate locations of the genes for Huntington's disease, Duchenne's muscular dystrophy, retinoblastoma (cancer of the eye in children), some forms of manic-depressive illness, cystic fibrosis, cancer of the colon, and Alzheimer's disease, as well as a number of other disorders.

Finding these genes will allow researchers to make copies of them for study, to understand their functions, to learn what protein product each gene makes, to define the precise mechanism of

causation of these disorders, to understand ways to treat disorders that arise from defects in these proteins, and perhaps even to replace defective genes. Mapping genes on the chromosomes of complex organisms and determining the order or sequence in which the chemical units of DNA are arranged represent major challenges. NIH is prepared to undertake these challenges in coordination with the other Federal agencies and research funding organizations represented here today, as well as with the university community and the biotechnology industry.

#### Evolution of the Human Genome Initiative

A brief comparison between the original outline for the OTA study and the final report serves to describe the evolution of thought concerning the human genome project that has taken place over the past two years. Early discussions of this proposal arose largely from the development of the automated DNA sequencer, the instrument that made it conceivable to consider sequencing the entire human genome from end to end.

At that time, the debate focused on the cost of obtaining the sequence rather than the usefulness of such information once it had been obtained. Using current technology, the project was estimated at \$3 billion based on a rate of \$1 per nucleotide. This price tag boosted biology into the realm of "big science," a notion that raised alarm in the scientific community.

While we may still be thinking about the costs, the nature of the project has changed, as indicated by the title of the OTA report, "Mapping Our Genes--The Genome Projects: How Big, How Fast?"

Instead of simply determining the order of the three billion bases of one person's DNA, the goal now is to locate and identify the roughly 100,000 genes that code for human proteins.

There are several types of maps of the human genome, including the sequence, which is a map of the highest level of resolution. Genetic maps, physical maps, and ordered libraries of DNA fragments will serve as useful tools for basic biologists and for the biotechnology industry long after they are completed.

Mapping genes makes sense both from a scientific standpoint, and from a public policy perspective. The DNA sequence provides the information necessary to synthesize a piece of DNA that can then be used as a probe to locate specific genes in situ, or to engineer it into bacteria or yeast in order to manufacture important proteins. But unless one also knows where the gene for that protein begins and ends, the sequence data is not useful for that purpose.

Many human genes have already been mapped to their respective chromosomes (about 1,400) but this represents a very small fraction of the total (1.4 percent if there are 100,000 genes). The genes that have been of special interest have been those that control the

structure of known substances, such as insulin or growth hormone, or are responsible for certain hereditary diseases, such as Sickle Cell Anemia.

As I mentioned earlier, in 1987 NIH devoted about \$110.5 million to projects in human genetics and genetic diseases, and an additional \$255 million per year to other studies of complex genomes in animal models. Comparable amounts in the President's FY 1989 budget request include \$443 million for total genome mapping efforts, of which \$128 million is for human genome projects. A portion of these sums is spent on mapping and sequencing, but it is important to stress that the existing research approach focuses on a limited number of widely scattered, but important genes. Moreover, these genes and other markers defining chromosomal loci are not evenly spaced along the chromosomes. The markers serve the same purpose as mile markers on a highway--if you pass mile marker number 20, you can easily find your location on a map. But, imagine how difficult it would be to get from one city to another if you didn't know how far apart they were or what other cities you would pass along the way. Using genetic measurement terms, if we had a map of each chromosome with markers evenly spaced, 1 centiMorgan (a relative unit of distance on a chromosome) apart, we could determine the location of genes that fell between the markers with almost 99 percent certainty.

Similarly, there are millions upon millions of nucleotides that will not be sequenced by the traditional approach. The OTA report



quotes David Botstein of Genentech, Inc., "[Sequencing the genome now] is like Lewis and Clark going to the Pacific one millimeter at a time." If they had done that, they would still be looking." Hence, in a strict analysis of cost and benefit, it is clear that the more markers there are available on each chromosome, the easier it is to determine the precise location of a specific gene.

It is also appropriate to note that unless information regarding the location of chromosome markers is shared among the scientific community, progress in mapping genes will be impeded. Competition between laboratories is healthy--it provides the incentive to keep moving and ensures validation of earlier work. But keeping results secret, or refusing to share biological material beyond publication harms the collective enterprise. NIH strongly encourages rapid exchange of information and biological materials among the research community.

These are the kinds of arguments that resulted in a consensus in the scientific community that construction of complete maps of the genomes of the human and other organisms is necessary to understand all of biology. The wealth of information that can be obtained from such maps make the genome project a very high priority effort.

Moreover, the historic commitment NIH has made to the fundamental research enterprise also provides the rationale for NIH to take that next step--constructing a map of the entire human genome. We clearly recognize the need to protect resources from being siphoned out of traditional efforts to support the new programs. At the

same time, it is only logical to provide for interchange between old and new so that the results of the genome initiative can be plugged into ongoing genetics research as quickly as possible. This is why we began discussing the appropriate role for NIH at a meeting of the Advisory Committee to the Director, NIH, in October 1986.

Advisory Committee to the Director, NIH, "The Human Genome"

I asked my Advisory Committee to examine a number of science and policy issues concerning the human genome. At that time, I emphasized NIH's strong commitment to peer-reviewed, investigator-initiated research projects. It is well recognized that this is the kind of research that led to proposals for a major effort to map and sequence the human genome.

Based upon views expressed by many of the participants, I stated publicly that NIH would not consider taking funds from ongoing investigator-initiated experiments in order to support a large-scale targeted program. However, two recent events have given NIH not only the opportunity but the responsibility to consider new plans without threatening our commitment to basic biomedical research. First, in Fiscal Year 1988, NIH received \$17.3 million of new monies specifically for funding a new research program in mapping complex genomes. Second, the President's budget request for NIH for Fiscal Year 1989 increases this amount to \$28 million.

These funds will support a scientific approach that is very different from the traditional research approach that I described earlier. Such research on specific genes is still of great interest and importance because of the insight it provides into disease states that are due to absent or defective genes. These studies will continue as before. However, the dedicated funds will be used to promote technological development of the tools that are necessary to map the human genome. The long-term goals will be the construction of detailed maps of the human genome and those of other organisms that will help to understand human biology.

NIH Ad Hoc Program Advisory Committee on Complex Genomes

Based on the message of support from Congress and the Administration and on recommendations in the National Academy of Sciences (NAS), National Research Council (NRC) report on "Mapping and Sequencing the Human Genome," I convened an NIH Ad Hoc Program Advisory Committee on Complex Genomes to help plan the best means for attaining these goals. On February 29-March 1 of this year, the top scientists in mapping, sequencing, and information science were asked to help pinpoint how NIH can best invest these resources, in order to meet the needs of researchers engaged in genomic analysis and to accelerate progress in this field. A number of congressional staff members were also invited to participate in this meeting. Several of the members of the NIH Ad Hoc Program Advisory Committee on Complex Genomes were also

involved in the development of the National Research Council's report, which provided a basis for discussion of the NIH role in a national effort.

At this meeting, NIH announced its intention to initiate a centrally coordinated, targeted effort to map and sequence the human genome. Furthermore, in order to provide a strong administrative structure to support this effort, I proposed establishing an Office of Human Genome Research in my Office, headed by a new Associate Director, and a chartered program advisory committee.

The Ad Hoc Program Advisory Committee unanimously endorsed this proposal. Many Committee members expressed their support for NIH embarking on a course that may stretch the scope of its portfolio, but is entirely complementary to its current goals and mission. Furthermore, citing its history of support for genetics research, it was agreed that NIH is the appropriate agency to make a major commitment to mapping the human genome.

The group also supported the concept of a Program Advisory Committee on the Human Genome as a standing body that would provide continuing review of the activities and progress of the Office of Human Genome Research. A report of the Ad Hoc Program Advisory Committee meeting is being developed and will be made available to the public when review is completed.



Based upon the recommendations of the Ad Hoc Committee, and the mandate NIH has received to go forward, execution of the plan to establish the Office of Human Genome Research is under way. In addition, a chartered Program Advisory Committee on the Human Genome is being established so that they may begin their duties as soon as possible.

#### Office of Human Genome Research

The NIH Office of Human Genome Research will have three major functions:

- o Coordination and Integration—Every NIH component is currently involved in some aspect of genomic analysis. The Office of Human Genome Research is not intended to supersede ongoing efforts within other NIH components, but to integrate those efforts into a cohesive plan. Thus, relationships must be fostered across several planes including: intra-NIH coordination; interagency coordination between NIH and other Federal agencies (DOE and NSF), and other research-funding organizations; collaboration with industry and academia; and international cooperation.
- o Planning—As do other trans-NIH coordinating committees, the Office of Human Genome Research, in concert with NIH Institute representatives, will link NIH-wide activities and will provide

a central role in the planning and implementation of the complex genome program. I expect to include both the extramural as well as the intramural programs in this effort.

- o Development of New Proposals—But most importantly, for the purpose of creating detailed genomic maps, there must be specific proposals with set goals, much as those described in the NRC report. For example, I would like to see a 1 centimorgan map developed as soon as possible. Some suggestions made at the October 1986 meeting of the Advisory Committee to the Director have not yet been realized, even though great strides have been taken since then. For example:
  - oo We still need better methods for cloning and separating large DNA fragments and for automating much of the laborious DNA purification and sequencing process.
  - oo \$3.8 million was appropriated to the National Library of Medicine in FY 1988 for a National Biotechnology Information Center. The Center will conduct some work that is relevant to improving access to mapping and sequencing data but there are still barriers to information analysis that require attention. I would be happy to expand on that issue if you would like. Dr. Donald Lindberg, Director of the National Library of Medicine, is present also if you have questions you would like to direct to him.

oo One goal will be to maximize the efficiency of information exchange regarding new mapping data, improved techniques for storage and handling of biological materials, and enhanced data processing and analysis. Therefore, centralized coordination will rely heavily on effective interactions with NIH Bureau, Institute and Division (BID) programs, as well as with other research funding organizations and the academic research community.

#### NIH Program Advisory Committee on the Human Genome

This proposal requires that research goals and long-range plans will be formulated with the guidance of the NIH Program Advisory Committee on the Human Genome. The Advisory Committee will be comprised of non-Federal employees with demonstrated expertise in the scientific disciplines related to genomic analysis. Of necessity, the membership of the NIH Program Advisory Committee on the Human Genome will represent a number of diverse research disciplines including, but not limited to, molecular genetics, physical chemistry, bioengineering, mathematics, and computer science.

In their capacity as advisors, the Committee will be asked to:

- o Identify opportunities to further advance characterization of the genetic material of many organisms;

- o Recommend initiatives that should be undertaken to promote the development of new technologies;
- o Advise on research directions;
- o Identify areas of research requiring additional effort; and
- o Propose administrative solutions to the resource and training needs of the research community, specific to genomic analysis.

NIH will solicit the advice of the most qualified individuals in the related disciplines in order to develop a scientific plan and administrative options for promoting rapid progress in methods in mapping and sequencing, and for managing the wealth of information emanating from these studies.

At a Senate hearing last September, several Federal agencies, including NIH and DOE, agreed that interagency coordination is desirable and could be effected through an existing subcommittee of the Domestic Policy Council. That group has been reorganized as a subcommittee of the FCCSET (Federal Coordinating Council on Science, Engineering, and Technology), Committee on Life Sciences. I suggested at that hearing that the interagency committee be expanded to include representatives of the academic and industrial research communities. This need will be addressed by including such representatives on our Program Advisory Committee.



NIH Working Group on the Human Genome

I also Established an NIH Working Group on the Human Genome, as a subcommittee of the Advisory Committee to the Director, NIH. It will play a key role in the complex genome program. As it has done since its inception, the Working Group will provide coordination among BID programs. Moreover, each member brings critical expertise contributing to the current knowledge base in molecular genetics, methods, and technologies applied to greater understanding in this area, and in the area of collection, analysis, and distribution of data.

Cooperation between the Office of Human Genome Research and the NIH Working Group will be essential to the continuing review of current NIH efforts in genomic analysis and to close gaps in areas deserving attention, avoid unnecessary duplication of effort, identify and address crosscutting problems, and ensure consensus on the major elements of an overall strategy.

The Office of Human Genome Research will provide a focus for activities leading to the development of methods and resources necessary to characterize genetic material. This centralized program will also protect the continued health of fundamental studies in molecular genetics that are not part of the targeted effort. Furthermore, the visibility accompanying this effort will help to insure funding stability throughout the duration of the program.

Naturally, there will be a great deal of interest in the genome initiative among the research community. The Office, with the support of the Program Advisory Committee, will maintain communications with scientists in the field and keep the public informed about this project.

#### Interagency Coordination

One of the key responsibilities for the Office will be to coordinate the NIH planning process with other Federal agencies and research funding institutions who are involved in the human genome initiative.

NIH provides the lion's share of the Federal investment in genomic analysis, based on a commitment to basic research leading to an understanding of human health and disease states. However, both DOE and NSF are research agencies with a history of supporting research programs that are relevant to the genome project.

Thus, there are already a number of joint projects under way that contribute to a national effort. At the working level, scientists funded by all three agencies are either working together directly or are collaborators. For example:

- o NIH funds researchers in the DOE National Laboratories (through grants to researchers employed by the University of California);

- o DOE houses and provides support to resources that NIH and NSF fund, (GenBank<sup>2</sup> and the human chromosome flow sorting facility); and
- o NSF has provided a great deal of support to the development of instrumentation that is being used to analyze genetic material. For example, NSF supported development of the automated DNA sequencer by Leroy Hood.

As the human genome project proceeds, these connections will grow as a natural expansion of this area of science.

In a more formal sense, discussions have already taken place with the Department of Energy concerning the need for interagency coordination. It is understood that each agency will have its own agenda based on mission and historic involvement in genetics research. However, we also recognize that there will be many more opportunities for collaborative efforts such as those mentioned earlier. We anticipate that the NIH Program Advisory Committee on the Human Genome will be instrumental in identifying specific areas of opportunity. DOE has a similar advisory mechanism.

However, this is a small field of science and there are a finite number of people who might serve on these committees. Obviously, if the number of advisory bodies proliferates much further, we will eventually stifle the rate of progress. Therefore, we have agreed to share the expertise of some individuals who will serve on both

advisory committees. In this way, we hope to promote rapid advances in genome research while providing for productive communications between the two agencies. It would be entirely appropriate for the National Science Foundation to participate in this effort, also.

It is important to remember that the genome initiative is still evolving and will require periodic assessment to ensure proper administration. With this in mind, I would also propose holding an annual symposium sponsored by participating agencies to review progress in the science, to identify areas of need, and to address policy questions such as adequacy of resources. One important issue that will require ongoing assessment is ease of access to information and biological materials. As the project proceeds, these resources will become more critical and they are already stretched to capacity in some cases. Another topic for discussion might be the social and ethical implications of the application of results from genome research.

Throughout the year, it would also be useful to convene scientific conferences on specific focused topics in order to disseminate results and to compare various technologies. Scientists funded by each agency would be encouraged to discuss their work informally at scientific conferences.

Undoubtedly, additional means for supporting a coordinated Federal effort will become apparent as the research progresses. Our



current strategies are specifically designed to encourage the development of new proposals and to allow them to be incorporated into future plans.

#### International Cooperation

In the genome initiative, as in virtually all of basic science, studies are being done in close collaboration with laboratories around the world. For example, much of the research into the genetic transmission of inherited disorders has been done using cell lines maintained and distributed worldwide by a laboratory in Paris (Centre d'Etude du Polymorphisme Humain). Nucleic acid sequence data are pooled through an international network consisting of GenBank<sup>2</sup> in the U.S., the European Molecular Biology Laboratory in Europe, and most recently, the DNA Databank of Japan.

International collaborations are particularly valuable to genetics research because the incidence of genetic diseases varies in specific populations. As a result, sharing biological materials and information is essential to the construction of the map of the human genome. Again, the Office of Human Genome Research will be expected to maintain liaison with similar entities in other countries.

Conclusion

In closing, I would like to thank you again for your interest in a most exciting area of biology. The genome initiative has been received with a measure of positive attention and enthusiasm that we find somewhat surprising for such a technically sophisticated subject, but certainly gratifying. I am sure that the rate of progress in unraveling the mysteries of inheritance will accelerate and expect that the results will guarantee continued broad support.

This concludes my statement, Mr. Chairman. I would be happy to answer any questions you and the members of the subcommittee may have.



# THE OUTLOOK FOR BIOMEDICAL RESEARCH\*

by

James B. Wyngaarden, M.D.\*\*

In the span of the past 50 years members of the Society of Investigative Dermatologists and the National Institutes of Health have been active participants in bringing about astonishing advances in knowledge. Last year the NIH observed its centennial, and in a variety of events paid tribute to the pioneering work of the scientists who founded the agency, those who nurtured it through its early years, and those who were responsible for its spectacular growth. Although our roots extend back to a small laboratory established in 1887 at an entry port for immigrants on Staten Island, the NIH as it is known today had its beginnings at about the same time the Society of Investigative Dermatologists was formed. As a preface to discussing the outlook for biomedical research in general and some of our current plans for research in skin diseases, I will sketch some of the relatively recent history of the NIH.

What we call the modern NIH had its beginnings at the end of World War II. Essentially all of the American bioscientists and clinical researchers had been mobilized in the war effort. This mobilization was accomplished by awarding grants and contracts to American academic institutions, hospitals, and independent laboratories for the conduct of research on health problems that were expected to be encountered by the members of the armed services. Some 500 such awards were made during the war years. About 250 medical projects were still active when the Office of Scientific Research and Development was disbanded in 1945. These ongoing projects were turned over to the then National Institute of Health for administration.

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\*Address presented at the 50th Anniversary Meeting of the Society of Investigative Dermatologists, Washington, D.C., April 29, 1988.

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That action, and the policy decisions that preceded it, put in place for the first time a broad Federal program for the support of biomedical research that was not linked to wartime necessity or to a specific disease. The action also had the effect of designating the NIH as the principal biomedical research arm of the Federal Government.

The idea of a general and continuing research partnership through grants and contracts awarded by the Government to non-Federal institutions was a new thing. No patterns existed for it, but in little more than a year after the passage of the authorizing legislation, a system was set in place that has stood the test of time and has served as a model for organizations over the world. The basic tenet of the research grants program was a total commitment that such a system should protect the integrity and the independence of the research worker and his freedom from control, direction, regimentation and outside interference. It was a fundamental principle that the projects to be supported be selected in open competition, and that in making decisions on awards the agency should rely to a substantial degree upon appraisals by non-Federal scientists. Thus the system was designed to utilize in a significant way the expertise of scientists throughout the nation, not only in the conception and conduct of the research, but also in the evaluation of research proposals.

Forty years later we continue to avoid central direction of research when it is at all possible to do so. My personal philosophy is that the most important thing the NIH can do over the years is to promote discovery. No study section or advisory committee or review board can sit around a table and say "now it's time to discover penicillin" or anything else. Our successes come from supporting good scientists and giving them freedom.

The rapid expansion of the NIH organization has mirrored public concern about specific diseases and general categories of health problems. The names of the twelve Institutes constitute a kind of catalog of such concerns, as can be seen in the names of the National Cancer Institute, the National Heart, Lung, and Blood Institute, the National Institute of Neurological and Communicative Disorders and Stroke, and of course the newest component, the National Institute of Arthritis and Musculoskeletal

and Skin Diseases. Although many of the Institutes were given disease-specific missions, our commitment to basic research has been sustained and is a substantial component in the programs of each of the Institutes. The skin diseases program, for example, supports clinical studies of the skin in normal and diseased states, as well as research on the molecular biology of skin and other basic investigation. In the early 1970s, the fraction of the total NIH budget devoted to basic research was no more than 45 percent. By 1980 this portion had reached 52 percent, and in 1986 it was 63 percent.

During recent years between 10 and 12 percent of our total budget has been spent for intramural research and training in NIH's own laboratories. About 2,500 scientists with doctoral degrees and as many as 3,500 trained support staff are engaged in our intramural programs.

Since the early 1950's, large numbers--an estimated 25,000--of young scientists have come to the intramural research laboratories of NIH under our fellowship and associate programs for periods of from a few to several years, and then they have moved on to universities, academic medical centers and industrial organizations. These NIH alumni enrich American science. The linkages that develop between scientists working together in the intramural programs at NIH often are lasting. Many scientists who move from NIH continue to collaborate with their former NIH colleagues, they return for seminars, or they invite NIH scientists to visit them in their extramural setting so that there is a pattern of continuous interaction and collaboration.

As large as the intramural program is, however, almost 90 percent of the NIH's budget is devoted to our extramural programs--to awards for research and research training and for the associated administrative costs. Thus, the largest amount, by far, of NIH research takes place in some 1650 universities, medical schools, research hospitals, foundations and industrial laboratories in the United States and in many other countries. More than 50,000 non-Federal scientists participate in research projects funded by the NIH. Currently more than 63 percent of all the health-related research in American universities and about 75 percent of all research in academic health centers is funded by the NIH.

The key mechanism used by NIH for support of biomedical research is the investigator-initiated project grant. These grants are awarded in response to proposals submitted by researchers who outline the questions they wish to study, who specify their research strategies and estimate their costs. For example, in Fiscal Year 1987 the NIAMS provided almost \$18 million for the support of 124 project grants for research on skin diseases. Project grants for studies across the spectrum of the biological sciences are by far the largest component of all our programs. Well over half, or more than 58 percent, of the total NIH budget proposed for 1989 is allocated to such investigator-initiated projects.

Continued availability of a supply of high quality scientists is a basic necessity of the biomedical research enterprise. In science the limiting factor is a human one. Thus it is our special responsibility as scientists, academicians, and administrators to help assure the future supply of trained scientists. This imperative was understood by the officials who established the extramural programs of the NIH. They considered research training grants to be as essential to real progress as research grants themselves. Although in the intervening years the training programs have not always been accorded the same favorable treatment as at the beginning, they continue to represent a substantial component of the NIH budget. The FY 1989 request calls for \$240 million for the support of more than 11,000 trainees.

In 1987 about 70 postdoctoral awards were made for research training in dermatology.

A consequence of the amazing progress that has been made by the current generation of scientists is the level of sophistication that will be required of their successors. In the biological sciences there has been a substantial broadening of the scope of research. We have totally new disciplines within the biosciences so that larger numbers of more highly trained investigators will be needed if we are to continue the pursuit of discovery in new areas, such as structural biology and molecular genetics.



The Government-University-Industry Research Roundtable, of the National Academy of Sciences, has been holding thoroughgoing discussions of the issues relating to the development, identification, recruitment and retention of science and engineering talent. In evaluating the talent pool, they predict that the demand for scientists and engineers will remain strong in both industry and academia, but that at the same time the number of Americans qualified for these careers may be declining.

This prediction is based in part on certain disturbing trends. First, the supply of 22-year-olds is projected to drop more than 25 percent before the end of the century. If even the current level of supply for industry and academia is to be maintained, a significant increase in the proportion of 22-year-olds attaining science and engineering degrees will be necessary. The Roundtable group estimated that to maintain the 1985 level into the 1990s, the degree award rate would have to increase by 30 percent.

Given the demographics of the last decade of the 20th century, it is abundantly clear that if the necessary talent is to be available for continuation and extension of the explosive progress in the biological sciences, we must attract a greater share of the young people in these fields. Serious attention must be given to finding ways to develop the abilities and interests of children in grade school. The early years are critical.

Secondary school is the period when decisions can begin and the choices made in high school become crucial with respect to future careers.

The undergraduate years take a heavy toll in the numbers of students who elect to pursue careers in the sciences. When the time comes for them to decide whether or not to go into graduate or professional school, a decisive factor is the student's perception of the opportunity offered by a particular career, versus the investment in time and dollars required to prepare for such a career.

Because the NIH is the source of funding for almost two-thirds of the biomedical research conducted in American universities, our programs have



come to be regarded as indicators of the level of biomedical research activity in the nation. For this reason we have stressed in our budget discussions with the Congress and within the Administration the importance of stability in funding of research project grants. A reasonable degree of predictability of research support is essential for institutions and for individual investigators if they are to attract and maintain productive teams of researchers. Furthermore, such stability can indicate to young people at critical stages in their careers that there is reasonable assurance that having completed the intensive training required for participation in today's scientific activity, they will be able to look forward to active careers in health related research.

In recent years the number and quality of research proposals have increased steadily and have outstripped our ability to fund them. The NIH budget has continued to grow in real terms by 2 percent per year since 1965, and 5 to 6 percent per year in the past 5 years. However, we now can fund only about one-third of the meritorious proposals.

The system is stable and morale is high as long as our annual appropriations permit a reasonable number of new awards each year in addition to providing for the continuing grants whose average term is between 3 and 4 years. But the amount of funding available for new awards is subject to both the level of continuing commitments and to the level of new appropriations. Essentially the amount available for new awards is what is left after continuing commitments are met. In times of constrained budgets a roller coaster effect can develop with regard to new and competing renewal grants, and this in turn can send minor panic through the system. We have not yet developed a means for "buffering" current and prospective grantees from the effects of sudden budget changes.

Notwithstanding our efforts to fine-tune the system, the level of funding continues to be the principal determinant of our ability to nurture the productivity of biomedical research in the United States. We are especially concerned about the effect on the young researcher who, after seven to ten years of post college training, has about a one in three chance of gaining independent funding from NIH.

In this connection it is pertinent to note that the President's budget request for Fiscal Year 1989 for NIH would support a total of 21,145 project grants. This is 960 more than the number of grants during the current year, and more than twice the 10,175 project grants we funded in 1970.

Within the portion of the budget that makes provision for project grants, the amount available for new and competing renewal proposals is a critically important element. The FY 1989 President's budget would permit a total of 5,761 new and competing renewal grants as compared with 6,052 that we estimate will be made during the current year.

A total of \$613 million is identified for AIDS research at NIH, and this represents an increase of \$164 million over FY 1988. The FY 1989 total for NIH would be \$7.123 billion, an increase of 6.8 percent over 1988, with 28 percent for AIDS research and 5.4 percent for all other research over the comparable 1988 figure.

Each component of the NIH participates in AIDS research activities. For example, skin eruption may be one of the first clinical signs of exposure to HIV infection, and it is known that the vast majority of AIDS patients develop one or more skin diseases. To pursue this new avenue of research, the NIAMS convened a workshop in late 1987 to review current information and to identify opportunities for future research on the coexistence of HIV infection and specific skin diseases. A program announcement was issued last month to encourage basic, clinical or epidemiologic research on the potential clinical value of using early skin manifestations as an indicator of exposure to HIV infection, and to improve treatment of skin diseases seen in HIV-infected patients.

Among the other research areas engaging the attention of many Institutes within NIH is biotechnology. The portion of our budget devoted to biotechnology has increased gradually over the past five years, and about 14 percent is now devoted to directly related research, and an additional 21 percent to the underlying science base and research training. The training activity is of key importance, for one of the most crucial

issues facing the biotechnology industry is the dearth of appropriately trained scientific personnel. NIH spends \$60 to \$70 million a year to train research scientists in skills related to biotechnology.

I wish to emphasize how important I feel it is that adequate numbers of able and well trained scientists be available for the foreseeable future needs. The situation is critical with respect to molecular and structural biologists, not only as to numbers but also as to breadth, depth, and overall excellence of training. The needs are not confined to biotechnology, and meeting them is of serious import in practically all areas of biomedical research. An example is an announcement issued last August by NIAMS to encourage further research in molecular biology of normal skin structure and function, as well as changes that occur in skin diseases. The research is to focus on the identification of normal skin genes and the mechanisms of their regulation and expression, and the altered genes and proteins associated with skin diseases and disorders. This knowledge should allow for better diagnosis of and therapies for patients with genetic and acquired skin diseases.

Throughout the scientific community new techniques in the manipulation of DNA and the development of new methods of automated processing of DNA are yielding large volumes of information regarding the human genome. Characterizing the entire human genome will have profound implications for understanding the more than 3,500 diseases that are known to involve a genetic defect. This knowledge will enhance our understanding of the normal processes of development by many fold.

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An expert committee of the National Academy of Sciences has urged an immediate beginning of a program to discover the location of every gene within human chromosomes. In a statement accompanying their report the Academy's committee stated its strong belief that "such a special effort in the next two decades will greatly enhance progress in human biology and medicine." They also emphasized the need to study the genetic make-up of other animal species to provide comparative data.

We have just established an Office of Research on the Human Genome, headed by a new Associate Director within the Office of the Director of NIH. The new office will have a coordination and integration function with regard to new as well as ongoing efforts within all components of NIH. The office will have responsibilities for development of new proposals as well. We are proceeding to charter an NIH Program Advisory Committee on the Human Genome. We intend to tap the best minds in the related disciplines in order to develop scientific plans and administrative options for promoting rapid progress in methods in mapping and sequencing, and for managing the wealth of information emanating from these studies.

With the enactment of the FY 1988 appropriation and the President's FY 1989 budget request we feel confident that we can proceed with the highly important human genome project without risking the possibility that it would become a competitor and siphon funding from our other vital programs.

In biotechnology, as well as in all other areas of our activity, the NIH is committed to adding to the fundamental biomedical knowledge base and to ensuring that this knowledge is translated into applications that will improve the health of the nation, as well as aid in its economic growth. For what the biosciences yield enhances the well-being of people here and, in fact, in all parts of the world. A broad description of the role of science in the life of people everywhere appears in an inscription within the dome of the Great Hall of the National Academy of Sciences in Washington. It reads "...To Science, Pilot of Industry, Conqueror of Disease, Multiplier of the Harvest, Explorer of the Universe, Revealer of Nature's Law and Eternal Guide to Truth."



Within science and technology the search for new measures for the diagnosis, treatment, and especially the prevention of human disease and disability is of preeminent concern. To answer the question implied by the title of my talk I am happy to say that the outlook for biomedical research is promising, and I that I consider it great good fortune to be associated with so vital an enterprise in this exciting and highly productive time. Continued commitment to that research and our nurture of the biomedical research enterprise will continue to be of surpassing importance to the success of that enterprise.

CURRENT OUTLOOK FOR BIOMEDICAL RESEARCH SUPPORT\*

by

James B. Wyngaarden, M.D.\*\*

My association with the National Institutes of Health during its recent centennial observance has stimulated my interest in the history of the 1880s. I have been impressed by the rapid expansion of knowledge that was taking place during those years. It was a time when new areas of human endeavor were being opened, and it was a period of remarkable scientific advances, particularly in chemistry, physics and biology.

Although medical science in the United States lagged behind the state of knowledge in Europe, the determination of American scientists to close the gap was evident in many ways, including the establishment in 1887 and 1888 of such organizations as the American Physiological Society, the Hygienic Laboratory that later became the NIH, and the American Pediatric Society. I am especially honored to have the opportunity to address the annual meeting of the members of the Pediatric Society during this centennial year of the organization, and offer my warmest congratulations to all of you on the occasion of this significant anniversary.

As background for comments on the outlook for biomedical research from the NIH viewpoint, I will trace briefly the development of the agency over the past half century. What we call the modern NIH had its beginnings at the end of World War II. Essentially all of the American bioscientists and clinical researchers had been mobilized in the war effort. This mobilization was accomplished by awarding grants and contracts to American academic institutions, hospitals, and independent laboratories for the conduct of research on health problems that were expected to be encountered by the

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\*Address presented at the annual meeting of the American Academy of Pediatrics and the American Pediatric Society, Washington, D.C., May 4, 1988.

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members of the armed services. Some 500 such awards were made during the war years. About 250 medical projects were still active when the wartime Office of Scientific Research and Development was disbanded in 1945. These ongoing projects were turned over to the then National Institute of Health for administration.

That action, and the policy decisions that preceded it, put in place for the first time a broad Federal program for the support of biomedical research that was not linked to wartime necessity or to a specific disease. The action also had the effect of designating the NIH as the principal biomedical research arm of the Federal Government.

The idea of a general and continuing research partnership through grants and contracts awarded by the Government to non-Federal institutions was a new thing. No patterns existed for it, but in little more than a year after the passage of the authorizing legislation, a system was set in place that has stood the test of time and has served as a model for organizations over the world. The basic tenet of the research grants program was a total commitment that such a system should protect the integrity and independence of the research worker and his freedom from control, direction, regimentation and outside interference. It was a fundamental principle that the projects to be supported be selected in open competition, and that in making decisions on awards the agency should rely to a substantial degree upon appraisals by non-Federal scientists. Thus the system was designed to utilize in a significant way the expertise of scientists throughout the nation, not only in the conception and conduct of the research, but also in the evaluation of research proposals.

Forty years later we continue to avoid central direction of research when it is at all possible to do so. My personal philosophy is that the most important thing the NIH can do over the years is to promote discovery. No study section or advisory committee or review board can sit around a table and say "now it's time to discover penicillin" or anything else. Our successes come from supporting good scientists and giving them freedom.

The rapid expansion of the NIH organization has mirrored public concern about specific diseases and general categories of health problems. The names of the twelve Institutes constitute a kind of catalog of such concerns, as can be seen in the names of the National Cancer Institute, the National Heart, Lung, and Blood Institute, and the National Institute of Child Health and Human Development. Although many of the Institutes were given disease-specific missions, our commitment to basic research has been sustained and is a substantial component in the programs of each of the Institutes. In the early 1970s, the fraction of the NIH budget devoted to basic research was no more than 45 percent. By 1980 this portion had reached 52 percent, and in 1986 it was 63 percent.

During recent years between 10 and 12 percent of our total budget has been spent for intramural research and training in NIH's own laboratories. About 2,500 scientists with doctoral degrees and as many as 3,500 trained support staff are engaged in our intramural programs.

Since the early 1950's, large numbers--an estimated 25,000--of young scientists have come to the intramural research laboratories of NIH under our fellowship and associate programs. They come for periods of from a few to several years and then they have moved on to universities, academic medical centers and industrial organizations. We believe that these NIH alumni enrich American science. The linkages that develop between scientists working together in the intramural programs at NIH often are lasting. As a rule, scientists who move from NIH continue to collaborate with their former NIH colleagues, they return for seminars, or they invite NIH scientists to visit them in their extramural setting so that there is a pattern of continuous interaction and collaboration.

As large as the intramural program is, however, almost 90 percent of the NIH's budget is devoted to our extramural programs--to awards for research and research training, and for the associated administrative costs. Thus, the largest amount, by far, of NIH research takes place in some 1650 universities, medical schools, research hospitals, foundations, and industrial laboratories in the United States and in many other countries. More than 50,000 non-Federal scientists participate in research projects



funded by the NIH. Currently more than 63 percent of all the health-related research in American universities and about 75 percent of all research in academic health centers is funded by the NIH.

The key mechanism used by NIH for support of biomedical research is the investigator-initiated project grant. These grants are awarded in response to proposals submitted by researchers who outline the questions they wish to study, who specify their research strategies and estimate their costs. For example, in the current fiscal year the NICHD expects to expend more than \$250 million in support of over 1525 project grants. The President's budget request for 1989 calls for \$265 million for the support of 1551 project grants. Such grants for studies across the spectrum of the biological sciences are by far the largest component of all our programs. Well over half, or more than 58 percent, of the total NIH budget proposed for 1989 is allocated to investigator-initiated projects.

But continued availability of a supply of high quality scientists is a basic necessity of the biomedical research enterprise. In science, the limiting factor is a human one. Thus, it is our special responsibility as scientists, academicians and administrators to help assure the future supply of trained scientists. This imperative was understood by the officials who established the extramural programs of the NIH. They considered research training grants to be as essential to real progress as research grants themselves. Although in the intervening years the training programs have not always been accorded the same favorable treatment as at the beginning, they continue to represent a substantial component of the NIH budget. The FY 1989 request calls for \$240 million for the support of more than 11,000 trainees. The request would provide funds for research training of 694 individuals under programs supported by the NICHD.

A consequence of the amazing progress that has been made by the current generation of scientists is the level of sophistication that will be required of their successors. In the biological sciences there has been a substantial broadening of the scope of research. We have totally new disciplines within the biosciences so that larger numbers of more highly

trained investigators will be needed if we are to continue the pursuit of discovery in new areas, such as structural biology and molecular genetics.

The Government-University-Industry Research Roundtable, of the National Academy of Sciences, has been holding thoroughgoing discussions of the issues relating to the development, identification, recruitment and retention of science and engineering talent. In evaluating the talent pool, they predict that the demand for scientists and engineers will remain strong in both industry and academia, but that at the same time the number of Americans qualified for these careers may be declining.

This prediction is based in part on certain disturbing trends. First, the supply of 22-year-olds is projected to drop more than 25 percent before the end of the century. If even the current level of supply for industry and academia is to be maintained, a significant increase in the proportion of 22-year-olds attaining science and engineering degrees will be necessary. The Roundtable group estimated that to maintain the 1985 level into the 1990s, the degree award rate would have to increase by 30 percent.

A special problem is posed by the predicted shortages of competent science and mathematics teachers in secondary schools, and with the evidence of the lack of achievement of U.S. students in mathematics. This has serious implications in the biosciences as well as in engineering.

Given the demographics of the last decade of the 20th century, it is abundantly clear that if the necessary talent is to be available for continuation and extension of the explosive progress in the biological sciences, we must attract a greater share of the young people in these fields. Serious attention must be given to finding ways to develop the abilities and interests of children in grade school. The early years are critical.

Secondary school is the period when decisions can begin and the choices made in high school become crucial with respect to future careers.

The undergraduate years take a heavy toll in the numbers of students who elect to pursue careers in the sciences. When the time comes for them to decide whether or not to go into graduate or professional school, we must recognize that a decisive factor is the student's perception of the opportunity offered by a particular career, versus the investment in time and dollars required to prepare for such a career.

Because the NIH is the source of funding for almost two-thirds of the biomedical research conducted in American universities, our programs have come to be regarded as indicators of the level of biomedical research activity in the nation. For this reason we have stressed in our budget discussions with the Congress and within the Administration the importance of stability in funding of research project grants. A reasonable degree of predictability of research support is essential for institutions and for individual investigators if they are to attract and maintain productive teams of researchers. Furthermore, such stability can indicate to young people at critical stages in their careers that there is reasonable assurance that having completed the intensive training that today's science requires, they will be able to look forward to active careers in health related research.

In recent years the number and quality of research proposals have increased steadily and have outstripped our ability to fund them, even though the NIH budget has continued to grow in real terms by 2 percent per year since 1965, and 5 to 6 percent per year in the past 5 years. We now can fund only about one-third of the meritorious proposals.

The system is stable and morale is high as long as our annual appropriations permit a reasonable number of new awards each year in addition to providing for the continuing grants, whose average term is between 3 and 4 years. But the amount of funding available for new awards is subject to both the level of continuing commitments and to the level of new appropriations. Essentially the amount available for new awards is what is left after continuing commitments are met. In times of constrained budgets a roller coaster effect can develop with regard to new and competing renewal grants, and this in turn can send minor panic through the system.



We have not yet developed a means for "buffering" current and prospective grantees from the effects of sudden budget changes.

It is essential to the vitality of the scientific enterprise and to the morale of the scientific community that young scientists be encouraged. In 1986 we announced a new program called FIRST awards--a modification that lengthens the initial awards from three to five years, and provides a total of \$350,000 direct costs for the five years. This is intended to obviate the need for too early reapplication for investigators who encounter difficulties in the first 18 months of the term of a grant. It will, we believe, encourage more creative and less defensive research applications.

Further, we have expanded the number and types of longer term support for outstanding mid-career scientists through a program called MERIT awards. This program will involve facilitated extensions of five-year awards for an additional three to five years on the basis of a detailed progress report rather than through reapplication.

Notwithstanding our efforts to fine-tune the system, the level of funding continues to be the principal determinant of our ability to nurture the productivity of biomedical research in the United States. We are especially concerned about the effect on the young researcher who, after seven to ten years of post college training, has about a one in three chance of gaining independent funding from NIH.

In this connection it is pertinent to note that the President's budget request for Fiscal Year 1989 for NIH would support a total of 21,145 project grants. This is 960 more than the number of grants during the current year, and more than twice the 10,175 project grants we funded in 1970.

Within the portion of the budget that makes provision for project grants, the amount available for new and competing renewal proposals is a critically important element. The FY 1989 President's budget would permit a total of 5,761 new and competing renewal grants as compared with 6,052 that we estimate will be made during the current year. The budget proposal



for the NICHD includes funding that would permit 449 new and competing renewals as compared with current total of 468.

A total of \$613 million is identified for AIDS research at NIH, and this represents an increase of \$164 million over FY 1988. The FY 1989 overall total for NIH would be \$7.123 billion, an increase of 6.8 percent over 1988, with 78 percent for AIDS research and 5.4 percent for all other research over the comparable 1988 amount. The increase for NICHD would be 5.4 percent, including funding for AIDS research.

As of April this year, the number of children with AIDS remained relatively small: some 923 children up to age 12 and about 250 more aged 13 to 19 have been reported to CDC since 1982. The number is growing rapidly, and it is estimated that by the end of 1991 there will be more than 3,000 American children 12 years of age and under with AIDS, and as many as 10,000 to 20,000 HIV-infected children.

In February 1988, the Secretary of Health and Human Services, Dr. Otis Bowen, established within the Department a special initiative on Pediatric HIV infection to ensure that all HHS agencies coordinate their efforts on this important problem. The Work Group established under this initiative, chaired by Dr. Antonia Novello, Deputy Director of the National Institute of Child Health and Human Development, includes representatives of some 13 HHS components--not only the agencies normally associated with the public health and medical response to the epidemic, but also agencies responsible for financial and social support of families of HIV-infected children. The group will review HHS regulations to identify barriers to eligibility or benefits from various programs; develop a coordinated research agenda to support innovations in service delivery and care for children with HIV disease; and explore prevention strategies that would minimize virus transmission from HIV-infected mothers to their children, as well as transmission among adolescents.

No matter how much the Federal Government may do in dealing with a problem as difficult and complicated as AIDS in children, most of the care and support these families need must come at the local level. Physicians

in their roles as health care providers and as community leaders must be relied upon to do a great deal, but their cooperation in research activities, such as clinical trials designed for children with AIDS, will be critically important.

In the context of a discussion of research on AIDS, I will mention an issue affecting such investigations--one that is of widespread importance to essentially every area of biomedical research. I refer to a problem that seems to be growing more threatening. It is the effort by small, often unrelenting groups to put an end to the use of animals as subjects of research. It has become highly politicized, and stepwise has effectively increased the cost of research through unreasonable application of basically meritorious reforms in standards for animal care and curtailment of the use of pound animals. In some areas of research the problem goes beyond expense. For example, the scarcity of chimpanzees already threatens development of a vaccine for AIDS, and any unnecessary restrictions on their use at this time becomes doubly serious.

Among the areas engaging the attention of many Institutes within NIH is biotechnology. The portion of our budget devoted to biotechnology has increased gradually over the past five years, and about 14 percent is now devoted to directly related research, and about 35 percent devoted to underlying basic research and research training related to biotechnology. The training activity is of key importance, for one of the most crucial issues facing the biotechnology industry is the dearth of appropriately trained scientific personnel. NIH spends 60 to \$70 million a year to train research scientists in skills related to biotechnology.

I wish to emphasize how important I feel it is that adequate numbers of able and well-trained scientists be available for the foreseeable future needs. The situation is critical with respect to molecular and structural biologists, not only as to numbers but also as to breadth, depth, and overall excellence of training. The needs are not confined to biotechnology, and meeting them is of serious import in practically all areas of biomedical research. Throughout the scientific community new techniques in the manipulation of DNA and the development of new methods of automated

processing of DNA are yielding large volumes of information regarding the human genome. Characterizing the entire human genome will have profound implications for understanding the more than 3,500 diseases that are known to involve a genetic defect. This knowledge will enhance our understanding of the normal processes of development by many fold.

In the NIH appropriation for FY 1988 an amount of \$17.3 million was earmarked for the genome mapping project, plus an additional \$3.8 million for establishment of a related biotechnology information center at the National Library of Medicine. The President's request for FY 1989 includes \$28 million for the mapping and \$4 million for the communications center. Through the 1988 appropriation and the FY 1989 President's budget, both the Congress and the Administration have sent a clear message that this is an important mission, that there are immediate and long-range implications for public health, and that mapping the human genome should begin at once.

An expert committee of the National Academy of Sciences has urged an immediate beginning of a program to discover the location of every gene within human chromosomes. In a statement accompanying their report the Academy's committee stated its strong belief that "Such a special effort in the next two decades will greatly enhance progress in human biology and medicine." They also emphasized the need to study the genetic make-up of other animal species to provide comparative data.

We have just established an Office of Research on the Human Genome, headed by a new Associate Director within the Office of the Director of NIH. The new office will have a coordination and integration function with regard to new as well as ongoing efforts within all components of NIH. The office will have responsibilities for development of new proposals as well. We are proceeding to charter an NIH Program Advisory Committee on the Human Genome. We intend to tap the best minds in the related disciplines in order to develop scientific plans and administrative options for promoting rapid progress in methods in mapping and sequencing, and for managing the wealth of information emanating from these studies.



With the enactment of the FY 1988 appropriation and the President's FY 1989 budget request, we feel confident that we can proceed with the highly important human genome project without risking the possibility that it would become a competitor and siphon funding from our other vital programs.

In biotechnology, as well as in all other areas of our activity, the NIH is committed to adding to the fundamental biomedical knowledge base and to ensuring that this knowledge is translated into applications that will improve the health of the nation, as well as aid in its economic growth. For what the biosciences yield enhances the well-being of people here and, in fact, in all parts of the world.

Within science and technology the search for new measures for the diagnosis, treatment, and especially the prevention of human disease and disability is of preeminent concern. To answer the question implied by the title of my talk, I am happy to say that the outlook for biomedical research is promising, and that I consider it great good fortune to be associated with so vital an enterprise in this exciting and highly productive time. Continued commitment to the search and nurture of the biomedical research enterprise will continue to be of surpassing importance to the success of that enterprise.

Our organizations have been participants in spectacularly successful efforts against disease and disability during an era of progress unlike any previous period in history, and that progress has opened new vistas of challenge and opportunity for further conquest. Lewis Thomas described this process provocatively by saying that, "In no other century of our brief existence have human beings learned so deeply, and so painfully, the extent and depth of their ignorance about nature."<sup>1</sup> Nobelist Christian DeDuke emphasized more recent accomplishments when he observed cautiously that, "Although it is always difficult to judge one's own time in historical perspective, one cannot help the feeling that the second half of this century will be remembered for one of the great breakthroughs of human knowledge--perhaps the greatest to date, as it concerns the basic



mechanisms of life."<sup>2</sup> Experience and logic, moreover, teach us that what we have seen is but a beginning.

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<sup>2</sup>De Duve, Christian, A Guided Tour of the Living Cell, Scientific American Books. New York, 1984, p. 17.

STATEMENT BY  
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DIRECTOR  
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AND CHAIRMAN  
BIOTECHNOLOGY SCIENCE COORDINATING COMMITTEE  
  
BEFORE THE  
  
HOUSE SCIENCE, SPACE, AND TECHNOLOGY  
SUBCOMMITTEE  
  
ON NATURAL RESOURCES,  
AGRICULTURE RESEARCH AND ENVIRONMENT  
  
MAY 5, 1988

Mr. Chairman and Members of the Subcommittee:

I am pleased to appear before you to discuss the role of several government groups in the oversight of biotechnology. This is an area in which oversight by the National Institutes of Health (NIH) Recombinant DNA Advisory Committee and several interagency committees has proved to be most effective.

#### Coordinated Framework for Regulation of Biotechnology

In April 1984, the Cabinet Council Working Group on Biotechnology was established in the Office of Science and Technology Policy to study and coordinate the Federal regulatory policy for the products of biotechnology. It was directed to review the Federal regulatory rules and procedures relating to biotechnology, including the function of the NIH Recombinant DNA Advisory Committee and its role in biotechnology commercialization and safety regulation. As a result, a "Proposal for a Coordinated Framework for Regulation of Biotechnology" was published in the Federal Register of December 31, 1984 and a final document was published on June 26, 1986. This document sets forth the overall policies of Federal agencies involved in the oversight of biotechnology research and products and outlines the general policy framework within which regulatory decisions will be made.

#### Biotechnology Science Coordinating Committee

As the oversight process evolved, the Biotechnology Science Coordinating Committee (BSCC) was established on October 30, 1985. The BSCC is a committee

of the Federal Coordinating Council for Science, Engineering and Technology, which is a statutory interagency coordinating mechanism within the Office of Science and Technology Policy, Executive Office of the President.

The BSCC was established (1) to provide an opportunity for interagency science policy coordination and guidance and for the exchange of information regarding the scientific aspects of biotechnology applications submitted to Federal research and regulatory agencies for approval; (2) promote consistency in the development of Federal agencies' review procedures and assessments; (3) facilitate continuing cooperation among Federal agencies on emerging scientific issues; and (4) identify gaps in scientific knowledge.

The charter authorizes the BSCC to receive information regarding the scientific aspects of biotechnology applications submitted to Federal research and regulatory agencies for approval, to conduct analysis of broad scientific issues that extend beyond those of any one agency, and to develop generic scientific recommendations that can be applied to similar, recurring applications. The BSCC is authorized to convene workshops and coordinate special studies related to scientific issues in biotechnology. The committee holds periodic public meetings.

The BSCC is composed of senior representatives of the Department of Agriculture (USDA), the Department of Health and Human Services, the Environmental Protection Agency (EPA), and the National Science Foundation (NSF). From its inception through 1987, the chairman of the BSCC was Dr. David Kingsbury, Assistant Director of the NSF for Biological, Behavioral and Social Sciences.



Under Dr. Kingsbury's leadership the BSCC evaluated a variety of issues related to the coordination and oversight of emerging biotechnology. In particular, the Committee considered the appropriateness of unified Federal guidelines, the adequacy of greenhouse/release guidelines, biotechnology activities in the international arena, and proposed changes to existing guidelines and regulations. Considerable effort was also spent in reviewing documents for a proposed coordinated framework for the regulation of biotechnology.

The committee was rechartered in October 1987 and the NIH Director was appointed chair on November 23, 1987.

On February 17 of this year, I chaired the first meeting of the rechartered BSCC. A number of topics were discussed including a follow-up to the National Academy of Sciences (NAS) report, "Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues"; the establishment and role of the Agricultural Biotechnology Research Advisory Committee; an NSF report on biotechnology research and development activities in industry, and a USDA proposed rule on control of confidential business information involving agricultural research and related responsibilities.

At its March 25 meeting, the BSCC discussed proposed revised EPA biotechnology regulations; the March 23-24, 1988 meeting of the Agricultural Biotechnology Research Advisory Committee; an update on activities of the Risk Assessment Subcommittee; and a draft pamphlet on biotechnology regulations prepared by the Industrial Biotechnology Association.

The BSCC is authorized to form subcommittees and working groups. Currently a Risk Assessment Subcommittee is undertaking an in-depth survey of Federal agencies to determine their procedures for conducting risk assessments of biotechnology products. The subcommittee plans to submit a report of its findings to the BSCC.

The BSCC is also considering an in-depth study to assess what scientific knowledge should underlie the Federal oversight and regulation of the environmental use of genetically engineered microorganisms.

In the international arena, at a meeting last month of national experts on safety in biotechnology sponsored by the Organization for Economic Cooperation and Development progress was made towards developing "Good Developmental Practices" (GDP) criteria for limited scale controlled field trials of organisms. GDP would refer to low or negligible risk organisms and the practices appropriate for their field testing. A draft U.S. document, "GDP General Principles," will be the starting point for this effort.

#### Historical Review of Guidelines for Recombinant DNA Research

The need for oversight of biotechnology was foreseen in 1973 in response to the concern of scientists involved in the development of recombinant DNA techniques. At their request, NAS formed a Committee on Recombinant DNA Molecules. This committee recommended that the Director, NIH, establish a committee (now the Recombinant DNA Advisory Committee) to (a) oversee a program to evaluate hypothetical risks, (b) develop procedures to minimize the spread of recombinant DNA molecules, and (c) recommend guidelines to be followed by

investigators. In addition, the report recommended that an international meeting be convened to review progress and discuss ways to deal with potential hazards.

The scientists at that meeting concluded that most recombinant DNA experiments should proceed, provided that appropriate containment is utilized. The conference report made general recommendations for matching levels of containment with levels of hypothetical hazard for various types of experiments. The NIH was then called upon to translate these broadly based recommendations into detailed guidelines for research. NIH was thus the first Federal agency to exercise oversight of experiments involving recombinant DNA. The original NIH Guidelines were issued in 1976 and have been revised periodically since then.

#### Release Into the Environment

I would like to summarize the evolution of the NIH Guidelines with regard to release into the environment of organisms containing recombinant DNA molecules. The original version of the Guidelines specified that five classes of experiments were "not to be initiated at the present time." Among these were experiments involving the deliberate release into the environment of any organism containing a recombinant DNA molecule. This prohibition was retained in the first revision, although exceptions to prohibited experiments were now permitted. By April 1982, however, experiments that were previously prohibited were placed in a new section entitled "Experiments that Require RAC Review and NIH and IBC (Institutional Biosafety Committee) Approval Before Initiation."

Included again in this category was deliberate release into the environment of any organism containing recombinant DNA. The procedures for approval remained the same, but use of the term "prohibited" was dropped.

The 1983 revision of the Guidelines incorporated new procedures for approval of field testing under certain specified conditions of certain plants modified by recombinant DNA techniques; these now require review by the RAC Plant Working Group, but no longer by the full RAC, prior to approval by NIH.

In August 1987, the following provision was added to the Guidelines:

"Any recombinant DNA experiment which according to these Guidelines requires approval by the National Institutes of Health (NIH), may be sent by the submitter to the NIH or to another Federal agency that has jurisdiction for review and approval. Once approval, or other applicable clearances, has been obtained from a Federal agency other than the NIH (whether the experiment is referred to that agency by the NIH, or sent directly there by the submitter), the experiment may proceed without the necessity for NIH review or approval. However, any experiment that involves the administration of gene therapy to human subjects (see Section III-A-4 of the Guidelines) may not proceed without prior review by the NIH Recombinant DNA Advisory Committee and NIH approval."

It is anticipated that most experiments involving release into the environment of organisms containing recombinant DNA will fall under the jurisdiction of other Federal agencies.



### The Role of Other Federal Agencies

The responsibilities of FDA, USDA, and EPA are determined by statute and are generally based on characteristics or uses of the end products.

The Toxic Substances Control Act (TSCA) authorizes the Environmental Protection Agency to acquire information on and regulate chemical substances and mixtures of chemical substances. The statute gives EPA jurisdiction over the manufacturing, processing, distribution, use, and disposal of chemical substances. TSCA's applicability to the regulation of microbial biotechnology products is based on the agency's interpretation that microbes are chemical substances under TSCA. The Federal Insecticide, Fungicide, and Rodenticide Act establishes authority over the distribution, sale, and use of all pesticide products, including microbial pesticides. Generally a pesticide must be registered with EPA in order to be distributed, sold, or used in the United States.

The United States Department of Agriculture (USDA) has the responsibility to assure the safety of agricultural research in the same way as NIH assures the safety of biomedical research. The USDA has broad regulatory authority to protect U.S. agriculture against threats to animal health and to prevent the introduction and dissemination of plant pests and noxious weeds. This authority is applied to the regulation of animal, veterinary biological products, plants, and microorganisms through animal quarantine laws, the Virus Serum Toxin Act, the Federal Plant Pest Act, and the Plant Quarantine Act.

The FDA's review of products, including those that employ specialized biotechnological techniques, is conducted in the light of the intended use of a product on a case-by-case basis. FDA regulates new drugs and biologics under the Food, Drug, and Cosmetic Act (FDCA). Manufacturers of new drugs and biologics must operate in conformance with current good manufacturing practice regulations. For new medical devices, including diagnostic devices for human use, either a premarket approval application or reclassification petition is required. The FDCA requires FDA preclearance of food additives, including those prepared using biotechnology.

Mr. Chairman, that concludes my prepared statement. I would be pleased to answer any questions you may have.



CONTRIBUTION OF NIH TO AEROSPACE MEDICINE\*

by

James B. Wyngaarden, M.D.\*\*

I am particularly pleased to have been invited to address this 59th Annual Scientific Meeting of the Aerospace Medical Association, and to bring to you personally, and on behalf of my colleagues at the National Institutes of Health, our greetings and best wishes as you near the conclusion of a rich program of scientific communication. I am mindful of the honor associated with being selected to give the Harry G. Armstrong Lecture, an honor I have appreciated even more as I have learned more about this talented and dedicated man, a former President of this Association. His life was indeed one of achievement and honor. I was reminded that Dr. (and General) Armstrong received in 1981, at the hands of the Administrator of the Federal Aviation Administration, the highest honor the civil aviation community can bestow--the Edward Warner Award, and at the time he was only the second American to receive the award. The other was Charles Lindbergh who was given the award posthumously.

The specific subject of my remarks today concerns the contributions by the National Institutes of Health to aerospace medicine. However, in addressing that subject I will of necessity speak more generally of the benefits of biomedical research as they extend to essentially all fields of human endeavor. I will also take the liberty of describing briefly to you some of our aims and activities at the NIH, as well as something of the organization itself.

Last year the NIH observed its centennial, and in a variety of events paid tribute to the pioneering work of the scientists who founded the agency, to those who nurtured it through the early years, to those who were responsible for its spectacular growth, and to those who continue there in

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\*Harry G. Armstrong Lecture at the Aerospace Medical Association's Annual Meeting, New Orleans, Louisiana, May 12, 1988.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



these exciting times. Our roots extend from a small laboratory established in 1887 at an entry port for immigrants on Staten Island, New York, and its mission was to apply the new science of microbiology to research in support of efforts to prevent a potential epidemic of cholera.

My association with the NIH centennial events has stimulated my interest in the history of the 1880s. An impressive expansion of knowledge was taking place during those years. It was a time when new areas of human endeavor were being opened and it was a period of remarkable scientific advances, particularly in chemistry, physics and biology. But it could reasonably be claimed that aerospace medicine had its beginnings at least a century before NIH began. In a brief article that appeared in the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION in late 1986, News Editor Phil Gunby described some of the aeronautical exploits of John Jeffries, M.D. In 1786 the Boston physician published what has been called the first book in the English language on aeronautics by an American. Its title was "A Narrative of Two Aerial Voyages.. with Meteorological Observations and Remarks by Doctor Jeffries, London."<sup>1</sup> He was said to be the first American to make a free flight in a balloon and the first balloonist to conduct scientific observations in flight. His death some 35 years later was attributed to inflammation from a hernia, said to have been "occasioned by great exertions in his first aerial voyage.

In the same article, Gunby told of the establishment in 1918 of a Medical Research Board to study "the effects on the aviator of the peculiar conditions involved in flying," particularly with respect to determining "the cause and nature of the failure, psychologic or physiologic, or both, on the part of the pilot which frequently precedes a fall."<sup>1</sup>

At the time the Research Board was formed in 1918, the forerunner to NIH, then called the Hygienic Laboratory, was a small government operation conducting its research entirely in-house, and thus limited in the scope of its activities to what could be done by the staff of less than 100, including all professional and non-professional personnel. Some of the accomplishments of that period were outstanding, however, including the work by Joseph Goldberger that virtually eliminated a devastating disease--

pellagra--through simple, safe and effective dietary means for cure and prevention.

Today's NIH conducts or supports the conduct of more than one-third of all health-related research in the United States, at a cost of more than \$5.5 billion in 1987. More than 60 percent of all such research conducted in American universities is funded from the NIH, and the NIH provides for the conduct of 75 percent of all health-related research in American medical schools.

The principal purpose of the NIH is to provide dynamic leadership in biomedical research, and one of its major responsibilities is to invest wisely the funds appropriated to it for the support and conduct of biomedical research. More than 80 percent of that investment is made through grants and contracts (mostly grants) awarded for the funding of research projects that comprise what we call the NIH extramural program. The instrument most frequently used by the NIH for the support of extramural research is the grant awarded for investigator-initiated research projects. Currently about 58 percent of the total NIH budget is used for the support of such grants. These awards are made in response to proposals initiated by scientists for research on topics of their own choice. The institution where the investigator-applicant is employed serves as the grantee or recipient of the awarded funds and is responsible for administering them. The average grant for investigator-initiated projects is made for a period of something over three years, and on the average for amounts of about \$180,000 per year. Currently NIH provides support for more than 20,000 research projects. Awards are made on the basis of competitive review, and the number of eligible applications is such that NIH is able to fund only about one-third of meritorious proposals. The difficult funding decisions are made in the peer review system that is in effect the cornerstone of the NIH extramural program. The procedure by which research and research training applications are judged for scientific merit and approved for possible funding rests essentially on the participation by non-Federal scientists. They, in effect, constitute the study section and other regular review committees on which we depend for evaluation.

The NIH peer review system has been called the single most effective means for ensuring that high-quality health related research is supported. It was formally established in 1946 when, following World War II, the NIH was given responsibility for continuation of the government-sponsored medical research that had been initiated during the course of the war. What we call the "modern NIH" came into being when the decision was made at the White House level to give the agency responsibility for the ongoing grants and to encourage the continuation of sponsoring research in America's universities, academic health centers, hospitals and other laboratories. The system was put in place to help the agency meet its responsibility for making optimal use of funds for the support of extramural research.

The idea of a general and continuing research partnership through grants and contracts awarded by the government to non-Federal institutions was a new thing. No patterns existed for it; but the system that was set up has stood the test of time and has served as a model in many different countries. It is built on the philosophy that such a system should protect the integrity and the independence of the research worker and assure his freedom from control, direction, regimentation and outside interference. We continue to insist that the projects to be supported be selected in open competition, and that in making decisions on awards we should rely to a substantial degree upon the appraisals by non-Federal scientists. Thus the system was designed to utilize in a significant way the expertise of scientists throughout the nation, not only in the conception and conduct of the research but also in the evaluation of research proposals. Forty years later we continue to avoid exercising central direction of research when it is at all possible to do so. My personal philosophy is that the most important thing that the NIH can do over the years is to promote discovery. No review committee or study section can sit around a table and say "now it's time to discover penicillin" or anything else. Our successes come from supporting good scientists and giving them freedom.

The rapid expansion of the NIH since the midforties has mirrored public concern about specific diseases and general categories of health problems. The names of the current twelve Institutes constitute a kind of



chronicle of such concerns, as can be seen in the names of the National Cancer Institute, the National Heart, Lung, and Blood Institute, the National Institute on Aging, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases. Although many of the Institutes were given disease-specific missions, our commitment to basic research has been sustained and is a substantial component in the programs of each of the Institutes.

During recent years between 10 and 12 percent of our total budget has been spent for intramural research and training in NIH's own laboratories. About 2,500 scientists with doctoral degrees and as many as 3,500 trained support staff are engaged in our intramural program.

Since the early 1950s, large numbers--estimated to be as many as 25,000--young scientists have come to the NIH under our fellowship and associate programs for periods of from a few to several years, and then have moved on to universities, academic medical centers, and industrial organizations. The linkages that develop between scientists working together in our intramural programs at NIH often are lasting. As a rule, scientists who move from NIH continue to collaborate with their former NIH colleagues--they return for seminars, or they invite our scientists to visit them in their laboratory setting so that there is a pattern of continuing interaction and collaboration.

As large as our intramural program is, however, the largest amount of NIH research, by far, takes place in some 1650 universities, medical schools, research hospitals, foundations and industrial laboratories in the United States, and to some extent in other countries. More than 50,000 non-Federal scientists participate in the more than 20,000 research projects funded by the NIH.

With that background I will turn to the more specific subject of the relationship of NIH programs to the concerns of this organization, specifically to the subject of space medicine.



In general program planning leading up to the development of the 1988 budget, the NIH was asked by the Office of the Assistant Secretary for Health to prepare a paper assessing the need for a program initiative in space medicine at NIH. We were asked to discuss the rationale for expanding, focusing, coordinating, or stabilizing the current level of investment, and also to include a discussion of the potential for collaboration with NASA, other government agencies or industry. My remarks today are based in part on our response to that request.

We took note of the anticipated increase in frequency of manned space flights and the expected dramatic increase in the duration of individual missions to accommodate program goals, anticipating, for example, that many of the missions now being planned may involve manned flights of 90 days or longer.

We also noted that the character of space missions will also be changing, and unlike the earlier flights comprised of small crews of highly selected astronauts, future missions would involve much broader segments of the population who will be subjected to increasingly longer periods in space.

While the potential for increased frequency and duration of space travel is clear, to date fewer than 250 individuals have actually experienced space flight so that biomedical data on the physiological and psychological responses to such activity is sparse. From this limited experience involving relatively short space flights, there has, however, emerged a hint of some potential health problems that may result from exposure to the conditions encountered in space. Data collected during flights have demonstrated that humans and other animals undergo profound physiological changes as a result of the microgravity environment that exists in space. Disturbances that extend throughout the body appear to be caused by three major physiological changes due to weightlessness: the shift of blood from the lower part of the body to the upper; the inactivity or "unloading" of muscle and bone; and disturbances caused by unfamiliar sensory inputs.

While the space environment provides a new variety of challenging health problems, the type of research required to address these problems does not differ in kind from the biomedical research conducted and supported by the NIH in fulfilling its broad mission to protect the health of the American people. The concepts, approaches, and methodology developed largely through the efforts of the NIH over the last four decades of medical research can be brought to bear effectively upon the health problems that are now beginning to be perceived as a result of space travel, and which undoubtedly will continue to emerge as man is exposed to the specialized environment of space for increasingly longer periods of time. The research capability of NIH could be applied to the problems of space medicine immediately and without disruption of the generic mission of NIH. In fact, the NIH is now supporting significant amounts of research of relevance to space medicine.

Some of the major areas of investigation include such topics as studies related to the disequilibrium syndrome. In this area a wide range of studies is being conducted to better understand the mechanisms that regulate cardiac and circulatory homeostasis. These studies include investigation of the mechanisms for regulation of central and regional blood volume, and examination of factors involved in neural control of the circulation.

Extensive investigation is being conducted on erythropoietin production, including how it relates to red cell mass and oxygen transport.

Research is also being conducted on the structure and function of the vestibular system in health and disease, encompassing studies on the perception of the position in space, orientation in a zero gravity environment, motion sickness, and the dynamics of changes in equilibrium following therapeutic intervention with surgery or drugs.

In another general area of inquiry, studies are being conducted using special model systems to clarify the mechanisms by which immobilization alters bone and mineral metabolism. The studies will test the possibility that as yet unidentified factors account for the enhanced bone resorption

which occurs during the development of immobilization osteoporosis. The studies will also compare the effects of immobilization with those of suspension (in which the limbs are mechanically unloaded but not immobilized) on calcium metabolism and bone formation and resorption. The results of these studies will be useful in determining the relative contributions of reduced mechanical stress and the action of bone resorbing cells to the development of immobilization osteoporosis.

Studies are also focusing on the transport of oxygen to tissues and organs under conditions of ambient hypoxia, and the relationship between tissue capillarity and diffusion distances in species native to high altitudes versus lowland species acclimatized to hypoxic conditions.

Similar studies are examining the pathophysiologic effects of hypoxia, particularly with regard to the mechanisms of chronic mountain sickness and control of the hematological response to hypoxia and environmental stress.

Additional studies are focusing on mechanisms responsible for changes in the control of breathing in man during long-term exposure to chronic hypoxia, with special emphasis on the role of the higher brain. Comparative studies of several very different respiratory systems (mammals, birds and reptiles) are providing new information on gas exchange and ventilatory control under various hypoxic conditions.

Investigations are being conducted to elucidate the mechanism of renal stone formation, particularly the kinetics of the stone forming process. Related studies aim to determine the mode of intestinal absorption of stone-forming substances, including the role of vitamin D in this process.

Research is being undertaken to evaluate the regulation of the synthesis of renal hormone found to be elevated in individuals with high urine calcium who form calcium-based kidney stones. Among the factors to be assessed are the effects of calcium and phosphate concentrations and of intestinal or other hormones.



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Other areas of NIH interest and activity encompass studies of the biological consequences of low-level ionizing radiation, including: the chemistry of the interaction of various kinds of radiation with cell molecules; the consequences of these actions with regard to cell function; the mechanisms of cellular repair of radiation damage to DNA; and variations in radiosensitivity between, for example, dividing and non-dividing cells.

Research is being conducted on the chemistry of the interactions between UV light and DNA, and the results of this interaction at the molecular, cellular and organismal level.

Research indirectly related to space medicine includes an array of different basic studies in cardiovascular physiology; vascular reactivity and blood pressure response in hypertension; the pathogenic mechanisms operating in disorders of bone formation, resorption and calcification; the origin, differentiation and regulation of bone-resorbing cells; bone mineralization as it relates to osteoporosis; cardiorespiratory adjustments of man submerged in deep water and under hyperbaric conditions; development of methods for detecting hereditary differences in sensitivity to radiation; and the effects of vitamins and other biological response modifiers in reducing damage from ultraviolet radiation.

In addition to the research studies I have mentioned, the NIH has another and equally important reason for maintaining a strong interest in space medicine, which stems from the potential contribution that research in space can make toward achieving the traditional mission of the NIH in dealing with health problems on earth. The novel environment encountered in space travel provides a "laboratory" in which studies and procedures can be performed which would be exceedingly difficult or impossible to achieve on the earth's surface.

Permit me to mention some examples:

- o Experiments in space offer promise of finding an explanation for the rapid deterioration of human blood. Deterioration of blood is thought to be caused by numerous factors, including cell damage from the



earth's gravitational pull that brings heavier elements of the blood to the bottom of blood storage bags. By studying blood in space, researchers can eliminate the effects of gravity, enabling them to determine other important factors in the deterioration of blood.

- o Many important biological materials--cells, enzymes and hormones--are currently being separated and purified by electrophoresis. But because earth's gravity exerts a negative influence on the separation process, only minute amounts can be extracted at one time. Processing in gravity-free space offers a means of separating biologicals in the large quantities and high levels of purity needed for research, clinical testing and pharmaceutical production.

These are but a few of the current scientific uses of the space environment. The specialized conditions of the space "laboratory" will afford increasing opportunities to pursue many more basic and applied studies which will capitalize on this unique research resource.

It is clear that the programs of NASA and NIH will both benefit greatly from increased cooperative efforts between the two agencies. NASA can obtain a better understanding of the health problems encountered in space travel, and the NIH has the potential to obtain new insights into the conventional health problems that fall within its purview.

We are now in the process of establishing an interagency working group between NASA and NIH with the intent of meeting on a regular basis to explore jointly the need for and feasibility of initiating a variety of cooperative and complementary programs and projects in order to advance knowledge in biomedical research. Examples of the cooperative programs to be discussed in the working group include:

- o The identification and possible development of complementary ground-based research programs by the two agencies in selected areas of biomedical research related to space flight. Initially we would expect to concentrate on programs in cardiopulmonary, neurovestibular, muscle, bone and radiobiology research. Programs in other disciplines may be developed at a later time if both agencies agree to do so.

- o The concurrent funding and management of focused university-based programs through the use of such existing mechanisms as program project awards or the formation of specialized centers of research.
- o The funding and management of career development awards in specific areas of biomedical research relevant to space flight.
- o The funding and management of graduate and postdoctoral fellowship awards in selected areas of biomedical research which require utilization of unique NASA or NIH facilities.
- o The formation of NASA or NIH Study Sections or Disciplinary Advisory Panels to conduct peer reviews of proposals in selected areas of biomedical research related to the interests of NASA and NIH.
- o The development of simplified administrative procedures to allow sharing of unique research facilities between NIH and NASA research teams.
- o The development of an interagency approval process to facilitate the space flight of NIH-sponsored research projects in the space station era. All such projects would utilize NASA-developed facilities.

The results of these discussions and cooperative activities should provide a more refined basis for program development. In the meantime, as a result of experience and through continuous informal assessments of advances in the state of knowledge in the life sciences related to space travel, there exists a set of broad goals, opportunities, and strategies for space life sciences research. The experience gained by NIH over the last four or five decades in providing support to establish and maintain the preeminence of the scientific enterprise in this country has served to establish a set of general principles of research support that could serve to assist in guiding the development of a national program of space life sciences research.

Permit me to turn now to the general outlook for biomedical research and to factors that will be of substantial consequence in whatever efforts we may pursue either jointly or individually.

Continued availability of a supply of high quality scientists is a basic necessity for the biomedical research enterprise. In science the limiting factor is a human one. Thus, it is our special challenge as scientists, as physicians, as academicians and administrators to help assure the future supply of trained scientists. This imperative was understood by the officials who established the extramural programs of the NIH. They considered research training grants to be as essential to real progress as research grants themselves. Although in the intervening years the training programs have not always been accorded the same favorable treatment by budget authorities as at the beginning, they continue to represent a substantial component of the NIH budget. The FY 1989 request calls for \$240 million for the support of more than 11,000 trainees.

One consequence of the amazing progress that has been made by the current generation of scientists is the level of sophistication that will be required of their successors. In the biological sciences there has been a substantial broadening of the scope of research. We have totally new disciplines within the biosciences so that larger numbers of more highly trained investigators will be needed if we are to continue the pursuit of discovery in new areas, such as structural biology, molecular genetics, and in the disciplines emerging in aerospace medicine.

It is predicted with confidence that the demand for scientists and engineers will remain strong in both industry and academia, but that at the same time the number of Americans qualified for these careers may be declining. This prediction is based, in part, on certain disturbing trends. First, the supply of 22-year-olds is expected to drop as much as 25 percent before the end of the century. If even the current level of supply for industry and academia is to be maintained, a significant increase in the proportion of 22-year-olds attaining science and engineering degrees will be necessary. It has been estimated by a group sponsored by

the National Academy of Sciences that to maintain the 1985 level into the 1990s the degree award rate would have to increase by 30 percent.

A special problem is posed by the predicted shortages of competent science and mathematics teachers in secondary schools, and with the evidence of the lack of achievement of U.S. students in mathematics. This has serious implications in the biosciences as well as in engineering.

Given the demographics of the last decade of the 20th century, it is abundantly clear that if the necessary talent is to be available for continuation and extension of the explosive progress in the biological sciences, we must attract a greater share of the young people into these fields. Serious attention must be given to finding ways to develop the abilities and interests of children in grade school. The early years are critical.

Secondary school is also a critical period for it is then when decisions and choices begin to be made--decisions that are crucial with respect to future careers. The undergraduate years in college take a heavy toll in the numbers of students who elect to pursue careers in the sciences. When their time comes to decide whether or not to go into graduate or professional school, we must recognize that a decisive factor is the student's perception of the opportunity offered by a particular career, versus the investment in time and dollars required to prepare for such a career.

Because the NIH is the source of funding for almost two-thirds of the biomedical research conducted in American universities, our programs have come to be regarded as indicators of the level of biomedical research activity in the nation. For this reason we have stressed in our budget discussions with the Congress and the within the Administration the importance of stability in funding of research project grants. A reasonable degree of predictability of research support is essential for institutions and for individual investigators if our academic centers are to attract and maintain productive teams of investigators. Furthermore, such stability can indicate to young people at critical stages in their careers that there



is reasonable assurance that having completed the intensive training that today's science requires, they will be able to look forward to active careers in health-related research. It is essential to the vitality of the scientific enterprise and to the morale of the scientific community that young scientists be encouraged.

There is another problem that I should mention. It is less fundamental, perhaps, than the continuing supply of scientists, but it is of importance to almost every area of biomedical research. I refer to a problem that seems to be growing more threatening. It is the effort by small, often unrelenting groups to put an end to the use of animals as subjects of research. It has become highly politicized, and stepwise has effectively increased the cost of research through insistence upon unreasonable application of basically meritorious reforms in standards for medical care and curtailment of the use of pound animals. In some areas of research the problem goes beyond expense. For example, the scarcity of chimpanzees already threatens development of a vaccine for AIDS, and any unnecessary restrictions on their use at this time becomes doubly serious.

To return to the theme of the future outlook for biomedical research, I must mention biotechnology--a subject engaging the attention of many of the components of the NIH. The portion of our budget devoted to biotechnology has increased gradually over the past five years and about 14 percent is now devoted to directly related research, with about 35 percent devoted to basic underlying research and research training related to biotechnology. The training activity is of key importance, for one of the most crucial issues facing the biotechnology industry is the dearth of appropriately trained scientific personnel. NIH spends \$60 to \$70 million a year to train research scientists in skills related to biotechnology.

The situation is critical with respect to molecular and structural biologists, not only as to numbers but also as to breadth, depth and overall excellence of training. Throughout the scientific community new techniques in the manipulation of DNA and the development of new methods of automated processing of DNA are yielding large volumes of information regarding the human genome. Characterizing the entire human genome will

have profound implications for understanding the more than 3,500 diseases that are known to involve a genetic defect. This knowledge will enhance our understanding of the normal processes of development by many fold.

In the NIH appropriation for FY 1988 an amount of \$17.3 million was earmarked for the genome mapping project, and the President's request for 1989 includes \$28 million for that purpose. Thus, through the FY 1988 appropriation and the FY 1989 President's budget, both the Congress and the Administration have sent a clear message that this is an important project and program, that there are immediate and long-range implications for public health, and that mapping the human genome should begin at once. Furthermore, these actions give us confidence that we can proceed with the highly important human genome project without risking the possibility that it would become an active competitor and siphon funding from our other vital programs.

We have established an Office of Research on the Human Genome, headed by a new Associate Director within the Office of the Director of NIH. The new office will have a coordination and integration function with regard to new as well as ongoing efforts within all components of NIH. The Office will have responsibility for development of new proposals as well. We are establishing an NIH Program Advisory Committee on the Human Genome. We intend to tap the best minds in the related disciplines in order to develop scientific plans and administrative options for promoting rapid progress in methods in mapping and sequencing, and for managing the wealth of information emanating from these studies.

Biomedical science has been the source of recent and spectacularly successful efforts against disease and disability during an era of progress unlike any previous period in history. That progress, in turn, has opened new vistas of challenge and opportunities for further conquest. Lewis Thomas described the progress provocatively by saying that, "In no other century of our brief existence have human beings learned so deeply, and so painfully, the extent and depth of their ignorance about nature."<sup>2</sup>

In calling this statement to the attention of audiences from time to time, I have paired it with a quotation from Nobelist Christian de Duve, who emphasized recent accomplishment when he observes that, "Although it is always difficult to judge one's own time in historical perspective, one cannot help the feeling that the second half of this century will be remembered for one of the great breakthroughs of human knowledge--perhaps the greatest to date, as it concerns the basic mechanisms of life."<sup>3</sup>

It is from such a platform that we launch into the undiscovered realm of rich benefits from biomedical research.

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<sup>1</sup>Gunby, Phil, Journal of the American Medical Association, Chicago, October 17, 1986, p. 2010.

<sup>2</sup>Thomas, Lewis, The Medusa and the Snail, The Viking Press, New York, 1979, p. 16.

<sup>3</sup>De Duve, Christian, A Guided Tour of the Living Cell, Scientific American Books, New York, 1984, p. 17.

## INTRODUCTORY REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

First of all, I have been asked to make an announcement. Immediately following the presentation by Dr. Koshland, Dr. Wylie Vale will present the Mathilde Solowey Lecture in the Neurosciences in this auditorium.

Following Dr. Vale's presentation, at about 5:00 p.m., there will be a reception sponsored by the FAES in the 2nd floor cafeteria area of the ACRF.

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Welcome to the annual R. E. Dyer Lecture. This lecture series was established in 1950 to honor the late Rolla Eugene Dyer upon his retirement as Director of the National Institutes of Health (NIH).

Dr. Dyer dedicated 34 years of service to the U.S. Public Health Service and NIH. Before introducing today's speaker, I would like to share with you some highlights of Dr. Dyer's career.

His first assignment when he joined the Public Health Service in 1916 was to conduct field studies of bubonic plague in New Orleans. Five years later he came to Washington to work in the Laboratory of Hygiene, from which the National Institute of Health evolved. He rose to become director of NIH's Division of Infectious Diseases, the forerunner of the National Institute of Allergy and Infectious Diseases, in 1936.

Dr. Dyer made many notable contributions to the field of infectious diseases research. Most significant was his work on endemic typhus. After finding the agent for the disease in the common rat flea, he showed how the disease was spread and helped develop a vaccine against it.

He also studied scarlet fever, influenza, and Rocky Mountain Spotted fever, and in 1940 showed that a "new disease" in the United States was in fact "Q" fever, previously found in Australia.

A respected administrator as well as an eminent scientist, Dr. Dyer was appointed Director of NIH in 1942. During his 8-year tenure, he oversaw a previously unparalleled period of growth and change. He organized the Division of Research Grants, planned for construction of the Clinical Center, and helped establish three new institutes: the National Heart Institute, the National Institute of Dental Research, and the National Institute of Mental Health. By the time he retired in 1950, NIH had pluralized its name and was well on its way to becoming the world's foremost center for biomedical research.

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\*For Dr. Marian E. Koshland on the occasion of the annual R. E. Dyer Lecture in Masur Auditorium on May 18, 1988.

\*\*Director, National Institutes of Health, Bethesda, Maryland 20892.



In recognition of Dr. Dyer's many significant contributions to NIH, the Dyer lecturer is personally selected by the NIH Director, with advice from his senior scientific staff. Each lecturer is an internationally recognized researcher whose scientific accomplishments pertain specifically to problems of infectious diseases.

Today's speaker, Dr. Marian Elliott Koshland, is distinctly worthy of that honor. She currently serves as chair of the Department of Microbiology and Immunology at the University of California, Berkeley, and is an esteemed immunologist.

Most recently, Dr. Koshland has developed a model system for studying how an immature cell, which has several potential developmental pathways, becomes a cell with a specialized function.

Particularly interesting to Dr. Koshland is how hormones influence this differentiation process. Her model system involves examining how binding of the hormone interleukin-2 to B-cell receptors signals the nucleus to turn on certain genes.

Dr. Koshland's interest in immunology developed shortly before the end of World War II during her junior year in college. After graduating from Vassar, she attended the University of Chicago, where she earned an M.S. in bacteriology and a Ph.D. in immunology. She carried out postdoctoral work at Harvard Medical School.

Subsequently, she worked briefly with the Manhattan District Atomic Bomb Project in Oak Ridge, Tennessee, and then at Brookhaven National Laboratory in Upton, New York.

She began working at Berkeley in 1965, and for many years concentrated on studying the structure and specificity of antibodies. In 1970, she was promoted to Professor of Immunology.

In the early 1970s she discovered a new structural protein in a particular class of antibodies. The discovery of this protein, since named the J chain, signalled an important contribution to immunology and a significant point in her career.

Dr. Koshland's continuous work on the J chain since its discovery has earned her worldwide recognition as a J-chain expert (and the nickname "Dr. J"). She has found that the J chain helps link basic y-shaped antibody units into larger immunoglobulins. In her model system of differentiation, she is studying how hormone binding turns the J chain gene on.

Among other honors and achievements, Dr. Koshland is a member of the National Academy of Sciences and past president of the American Association of Immunologists. She has served on the President's Biomedical Research Panel and the National Science Board of the National Science Foundation. For her distinguished service to NIH--including membership on both the Advisory Committee to the Director, NIH, and NIAID's Allergy and Immunology Study Section--she received the NIH Merit Award. She is also a past and present editorial board member of several leading biomedical journals.

INTRODUCTORY REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

Once again the Foundation for Advanced Education in the Sciences has performed a valuable service for the NIH community, and through it to science in general by arranging for this colloquium on scientific authorship, a subject of interest and importance to all of us.

More than most professional activities, biomedical research is dependant upon published literature. The principal channels of communication among investigators in the biosciences are the columns of the two to three thousand scholarly journals in which reports of biomedical research are published. Scientific publication is both a mechanism for communicating new results and a contribution to a priceless repository of data, which later may be retrieved and used in new ways that had not been considered at the time of original publication. Such publication is, in fact, a part of the research process itself, for there is validity in the well-worn aphorism that "research is not completed until a report of its results has been published."

In his book "Megatrends," John Naisbett claimed that six to seven thousand scientific articles are written each day, and that scientific and technical information increases at the rate of 13 percent each year.<sup>1</sup> He was referring to all scientific disciplines, but the expansion in the biosciences is keeping pace if not surpassing other disciplines in the number of scientific articles published. It is fortunate that new advances in computer and communications technologies are helping us to make increasing use of the valuable content of the information explosion.

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\*Presented at the Foundation for Advanced Education in the Sciences Colloquium on Scientific Authorship: Rights and Responsibilities, Lipsett Auditorium, Bethesda, Maryland, May 31, 1988.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

The momentum of discovery in science, even in this time of remarkable progress, is, as always, dependent upon new increments of knowledge that lead to better understanding of larger questions. They are the basic materials from which ultimately, through refinement and combination with other findings, important fundamental insights can be gained, or new means of treatment, diagnosis or prevention will be developed. In dealing with the rapidly expanding volume of information the investigator must exercise critical evaluative judgements. The significance of such clues as the scientific reputation of the authors and of the journal becomes more critical when the range of readily available material is greatly expanded. Some have warned of the danger that a kind of Greshams law can operate in the forums where scientific information is exchanged to the detriment of essential communication.

Scientific communication is a continuing activity. As the body of knowledge about a given subject matures, it constantly is being refined in a process driven by the flow of new information. The channels for this information must be kept clear of the spurious so that the genuine can flow without impediment. A cogent observation on this subject was by a modern novelist who wrote, "When you trade in information (as contrasted with knowledge), you have stock that has a very short shelf life. Unlike brandy, information cheapens with age."<sup>2</sup> Ironically, one of the prime functions of scientific communications is to modify and correct that which already has been communicated.

Again I will emphasize the thought that communication among scientists is an integral part of research activity. It would virtually be impossible today for an investigator to pursue successfully a research question from its conception to its fruition without reference to undistorted and complete records of the work of other scientists.

Thus, the avoidance of contamination is as important in channels of scientific communications as it is in the laboratory. To that end, the FAES has served the cause of biomedical research by arranging for the exchanges that will follow today.

REFERENCES

<sup>1</sup>Naisbitt, John, "Megatrends, Warner Books, New York, 1984, p. 16.

<sup>2</sup>Whitaker, Rodney, (Trevanian), "Shibumi," Crown Press, New York, 1979.





## REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

When the NIH Honor Awards Ceremony was held last year we were looking forward to the closing months of a full and varied schedule of events held in observance of our centennial. My remarks preceding the awards in the 1987 ceremony consisted mainly of references to some of the individuals whose accomplishments have become valued components of the tradition we inherit. One purpose of discussing these bits of history was to provide a foretaste of the challenges and excitement to come in the second century of the NIH. In focusing on highlights of the past, however, there is always the possibility we may not see clearly the significance of the events in which we currently are involved.

As members of a community such as ours it is not unusual that we sometimes are given to regarding one or another passage in our institution's history as the Golden Age, and to view the current scene less favorably. This phenomenon was commented upon by MIT Dean George Russell Harrison, who explained that certain periods in history appear golden from a distance because the intervening years absorb the blue and indigo hues.<sup>1</sup>

The message of this award ceremony, however, is one of assurance that the people of NIH continue to perform with the remarkable ability and dedication that through the years have been responsible for our finest hours of accomplishment. The message is also one of optimism about what can take place in the years ahead, a message made even stronger by the fact that those who will receive awards today are merely representative of the many who are equally as deserving.

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\*Presented at the NIH Honors Awards Ceremony,  
Bethesda, Maryland, June 6, 1988.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

I call your attention to the printed program for this ceremony. In the program are listed the recipients of today's awards, together with the formal statement as to why each honor is being given. Since the citations will not be read from the platform, you may wish to follow along as the awards are handed out.

Taken together these citations outline the range and variety of the activities of the personnel of this remarkable institution. Individually they speak of the enthusiasm with which the people of NIH go about performing their personal part of the vastly important task to which we have given ourselves.

Permit me to tell you a bit about the awards we will be presenting today.

The NIH Director's Award recognizes superior performance or special efforts significantly beyond the regular duty requirements, and directly relates to carrying out the NIH mission. There are three general categories of performance for which Director's awards are given: included in the first are intramural activities of a scientific or medical nature; extramural and administrative activities are the subject of a second category of awards; and the third recognizes technical, clerical, and other support services.

Outstanding Service Medals are awarded to officers in the Commissioned Corps of the U. S. Public Health Service who have either demonstrated outstanding continuous leadership in carrying out the mission of the PHS; or have performed a single accomplishment which has had a major effect on the health of the nation; or have performed a heroic act resulting in the preservation of health or property.

The NIH EEO Award of the year is given to the recipient selected from NIH personnel who received EEO Special Achievement Awards in their major organizational component during the preceding calendar year. Selection factors include the candidates' on-the-job employment opportunity contributions, also contributions made when such activities are

unrelated to performance of appointed position requirements. Other selection factors include outside activities, and the scope of the impact of their EEO contributions on their own organization and on the NIH as a whole.

A special award is made in recognition of the efforts and achievements of the late Harvey J. Bullock, Jr. All NIH employees except EEO program leaders are eligible for consideration for the Bullock award on the basis of their individual efforts in furthering equal opportunity, for their efforts in establishing or strengthening communication between employees and management in furtherance of excellence, equality or equity of employees, contributions that have increased the sensitivity of management to employee concerns, or activities that have had an impact on upward mobility efforts.

At the opening of my remarks I mentioned the NIH centennial celebration and noted the challenges we face, now that we are well launched into the second century. With this thought in mind I will close with an anecdote told by President John F. Kennedy, when just a month before his death he addressed the Assembly observing the Centennial of the National Academy of Sciences. He spoke of the urgency of going about the business of research, particularly basic research, and he told the story of how the "great French Marshal Lyautey once said to his gardener: "Plant a tree tomorrow," and the gardener said, "It won't bear fruit for a hundred years." "In that case," Lyautey said to the gardener, "plant it this afternoon." That is also a message for the second century of science for health.<sup>2</sup>

#### REFERENCES

<sup>1</sup> Harrison, George Russell; The Role of Science in Our Modern World, William Morrow and Company, New York, 1956 p. 245.

<sup>2</sup> Kennedy, President John F., The Scientific Endeavor: Centennial Celebration of the National Academy of Sciences, The Rockefeller Institute Press, New York, N. Y. 1965, p. 319.





## OPENING REMARKS\*

BY

JAMES B. WYNGAARDEN\*\*

IT IS LIKELY THAT MANY PERSONS IN THIS ROOM BELONG TO AN UNREASONABLE NUMBER OF ORGANIZATIONS, AND PROBABLY AT ONE TIME OR ANOTHER EACH OF US HAS VOWED TO RESIGN AT LEAST HALF OF HIS OR HER CURRENT MEMBERSHIPS. KNOWING THAT THIS IS TRUE OF THOSE WHO HAVE GATHERED HERE TELLS ME THAT YOU SEE A SERIOUS PURPOSE FOR THE NIH ALUMNI ASSOCIATION AND ARE WILLING TO DEVOTE TIME YOU CANNOT AFFORD TO ITS OBJECTIVES.

FOR THAT REASON I AM ESPECIALLY PLEASED TO HAVE AN OPPORTUNITY TO EXPRESS MY GRATITUDE FOR THE UNSELFISH AND PERSISTENT EFFORTS THAT HAVE BROUGHT US TO THIS POINT IN ORGANIZATION OF AN INTERNATIONAL NIH ALUMNI ASSOCIATION. ALTHOUGH ON MANY OCCASIONS WE HAVE REMARKED ON THE SIMILARITIES BETWEEN NIH AND INSTITUTIONS OF HIGHER LEARNING, I MUST SAY THAT FORMING AN ALUMNI ASSOCIATION HERE DOES NOT FIT READILY INTO ANY EXISTING ACADEMIC PATTERN.

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\*PRESENTED AT THE FIRST MEETING OF THE WASHINGTON AREA CHAPTER OF THE NIH ALUMNI ASSOCIATION AT THE CLOISTERS, BETHESDA, MARYLAND, JUNE 9, 1988.

\*\*DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND.

THE FIRST NIH ALUMNI REUNION WAS HELD APRIL 1975. ALL CONCERNED FELT THE EVENT WAS SUCCESSFUL, PARTICULARLY AS A PIONEERING VENTURE. IN ITS CLOSING HOURS A MEETING WAS HELD FOR THE PURPOSE OF CREATING A PERMANENT ORGANIZATION. OFFICERS WERE ELECTED AND THEY WERE GIVEN ACCESS TO A MAILING LIST OF SOME 5000 NAMES THAT HAD BEEN DEVELOPED IN THE COURSE OF PLANNING FOR THE HOMECOMING. THE DECISION WAS MADE TO PUBLISH A NEWSLETTER, AND IN TIME ONE WAS DEVELOPED THAT WAS PRODUCED ON AN IRREGULAR BASIS AND MAILED TO THE ALUMNI FOR WHOM WE HAD ADDRESSES. FINALLY THE NEWSLETTER WAS DISCONTINUED, AND AS A RESULT THE MAILING LIST BEGAN TO UNDERGO THE STEADY DETERIORATION TO WHICH ALL SUCH LISTS ARE PRONE WHEN NOT REGULARLY USED. THE MOBILITY OF NIH ALUMNI IS SUCH THAT A MAILING LIST CAN QUICKLY BECOME OBSOLETE UNLESS IT IS CONSTANTLY UPDATED.

THE NEED FOR A CURRENT LISTING BECAME PAINFULLY APPARENT WHEN WE DECIDED TO HOLD AN ALUMNI REUNION AS ONE OF THE HIGHLIGHT EVENTS OF THE NIH CENTENNIAL OBSERVANCE. JOHN EBERHART, PHIL CHEN, AND THEIR STAFFS TOOK THE LEAD IN WHAT TURNED OUT TO BE A SUBSTANTIAL TASK, THE DE NOVO IDENTIFICATION OF 7,000 NIH ALUMNI, COMPLETE WITH ADDRESSES. THIS BASIC CENTENNIAL LIST AUGMENTED BY THE ADDITION OF NAMES PICKED UP AT THE REUNION WILL GIVE THE ASSOCIATION A VALUABLE FOUNDATION ON WHICH TO BUILD. FURTHER, I UNDERSTAND THAT AN ARRANGEMENT IS BEING DEVELOPED WITH THE DIVISION OF PERSONNEL MANAGEMENT SO THAT WE CAN KEEP UP WITH NEW ALUMNI. AT THE TIME OF THEIR DEPARTURE EACH PERSON WHO LEAVES THE NIH WILL BE GIVEN A BRIEF STATEMENT ABOUT THE ALUMNI

ASSOCIATION, AND WILL BE ASKED IF THEY WISH TO JOIN OR IF THEY WISH TO LEAVE AN ADDRESS FOR RECEIVING ADDITIONAL INFORMATION ABOUT THE ASSOCIATION. AS THE LIST GROWS IT IS INCREASINGLY IMPORTANT THAT IT BE USED, IF NOT FOR A FORMAL NEWSLETTER, AT LEAST FOR MAILINGS ON A MORE OR LESS REGULAR BASIS. THE LESSON FROM OUR FIRST ATTEMPT TO SET UP AN NIH ALUMNI ORGANIZATION IS THAT IT MUST BE ACTIVE IF IT IS TO LIVE.

THIS MEETING IS AN ENCOURAGING SIGN OF ACTIVE LIFE, FOR WITH THE ESTABLISHMENT OF THE WASHINGTON AREA CHAPTER A KEY AND ESSENTIAL STEP HAS BEEN TAKEN TOWARD THE CREATION OF AN OVERALL ORGANIZATION.

WHEN LOCAL ALUMNI CHAPTERS HAVE BEEN ESTABLISHED IN CITIES THROUGHOUT THE COUNTRY AND ELSEWHERE, IT WILL BECOME POSSIBLE TO OPEN HIGHLY USEFUL AND UNIQUELY ORIENTED CHANNELS OF COMMUNICATIONS WITH OUR ALUMNI, WHO, IN FACT, CONSTITUTE AN IMPORTANT SEGMENT OF THE BIOMEDICAL RESEARCH COMMUNITY. THROUGH SUCH CHANNELS WE WILL BE ABLE TO CARRY ON FULL DISCUSSIONS WITH PERSONS OUTSIDE OF GOVERNMENT, WHO KNOW AND UNDERSTAND NIH AND CAN GIVE FRANK ADVICE TO US ON SUCH ISSUES AS HEALTH POLICY AND ITS APPLICATION TO RESEARCH, DISEASE PREVENTION, DISEASE CONTROL AND BIOTECHNOLOGY. THE LINKAGES CAN ALSO SERVE IN HELPING US TO KEEP UP WITH THE CAREER PROGRESS AND ACCOMPLISHMENTS OF OUR FORMER CO-WORKERS. THIS INFORMATION IS INTERESTING TO ALL OF US, AND ON OCCASION IS HIGHLY USEFUL AS WE SEEK TO EXPLAIN TO THE CONGRESS AND THE ADMINISTRATION THE WORTH OF CERTAIN OF OUR



ROGRAMS SUCH AS INTRAMURAL TRAINING. IT NOW IS DIFFICULT, IF NOT IMPOSSIBLE, TO OBTAIN IN MORE THAN FRAGMENTS OF INFORMATION ABOUT OUR FORMER COLLEAGUES. FURTHER, THE LOCAL CHAPTERS CAN BE OF INVALUABLE ASSISTANCE TO INTRAMURAL SCIENTISTS IN HELPING US TO IDENTIFY YOUNG AND PROMISING RESEARCHERS WHO MIGHT WISH TO STUDY AND TRAIN AT NIH. THEY ALSO COULD ACT ON OUR BEHALF IN INTERVIEWING LOCAL STUDENTS WHO WISH TO SPEND A SUMMER OR A SCHOOL YEAR AT NIH. THEY ALSO COULD BE OF GREAT ASSISTANCE IN SPONSORING SPECIAL EVENTS IN DIFFERENT LOCALITIES. ALL OF THIS IN ADDITION TO THE OPPORTUNITY SUCH AN ORGANIZATION GIVES FOR OLD FRIENDS AND COLLEAGUES TO GET TOGETHER.

IN THE TIME THAT REMAINS, I WOULD BE HAPPY TO ANSWER ANY QUESTIONS YOU MAY HAVE, PERHAPS WITH REGARD TO CURRENT NIH ISSUES--FOR EXAMPLE, THE NEW INITIATIVE ON THE HUMAN GENOME OR THE NEW OFFICE OF AIDS RESEARCH.

OPENING REMARKS: THE HEALTH OF BIOMEDICAL RESEARCH INSTITUTIONS:  
REPORT OF THE REGIONAL MEETINGS

INTRODUCTION

- o Good Morning. Before moving on to the business of the day, it is a pleasure to welcome several new members of the Advisory Committee. Joining us today are:
  - oo Mr. Peter Preuss, President, Preuss Foundation, Inc.
  - oo Dr. Peter H. von Hippel, Professor of Chemistry, Institute of Molecular Biology, University of Oregon
  - oo Dr. Helen K. Grace, Program Director, W.K. Kellogg Foundation
- o I would also like to take this opportunity to express my appreciation to Dr. John M. Bishop, Professor of Microbiology, University of California at San Francisco, Dr. Arthur C. Guyton, Professor and Chairman, Department of Physiology and Biophysics, Medical Center, University of Mississippi, Dr. David M. Kipnis, Busch Professor and

*Cum gratias*



Chairman, Department of Medicine, School of Medicine, Washington University, Dr. Carol M. Newton, Professor and Chairman, Department of Biomathematics, University of California, Los Angeles, and Dr. John Urquhart, President, APREX Corporation, Palo Alto who are attending their last meeting after having contributed greatly to the work of this Committee for the past several years.

- o Also, participating for the first time as representatives of their respective National Advisory Councils are:
  - oo Dr. Mary O. Amdur, Energy Laboratory and Department of Applied Biological Sciences, MIT (National Advisory Environmental Health Sciences Council)
  - oo Dr. Charles D. Bluestone, Director, Department of Otolaryngology, Children's Hospital of Pittsburgh (National Advisory Neurological and Communicative Disorders and Stroke Council)
  - oo Dr. James L. Boyer, Director, Division of Digestive Diseases, Yale University, School of Medicine (National Diabetes and Digestive and Kidney Diseases Advisory Council)

- oo Dr. John T. Flynn, Professor, Bascom Palmer Eye  
Institute (National Advisory Eye Council)
  
- oo Dr. Doris A. Howell, Professor of Pediatrics,  
School of Medicine, University of California, San  
Diego (National Center for Nursing Research  
Advisory Council)
  
- oo Dr. William McHugh, Director, Eastman Dental Center  
(National Advisory Dental Research Council)
  
- oo Dr. Palmer W. Taylor, Professor and Chairman,  
Department of Pharmacology, School of Medicine,  
University of California, San Diego (National  
Advisory General Medical Sciences Council)
  
- oo Dr. Joseph B. Warshaw, Professor and Chairman,  
Department of Pediatrics, School of Medicine, Yale  
University (National Advisory Child Health and  
Human Development Council)
  
- oo Dr. Hans Weill, Professor of Medicine, Tulane  
Medical Center (National Heart, Lung, and Blood  
Advisory Council)



An

- o In addition, I would like to welcome ~~two~~ additional members~~#~~ of the Division of Research Resources National Advisory Council who <sup>is</sup> ~~are~~ attending today's meeting-- Norman C. Francis, J.D., President of Xavier University of Louisiana and ~~Dr. Franklin M. Loew, Dean, School of Veterinary Medicine, Tufts University,~~ *(unavailable)* and a member of the National Advisory Council on Aging, Dr. John Papaconstantinou, Director, Division of Cell Biology at the University of Texas Medical Branch, Galveston.
- o Before proceeding to our topic of discussion today, I will report briefly on activities undertaken and planned as a followup to our last meeting on "The Role of Biomedical Research in Combating AIDS."
- o Since that meeting a number of steps have been taken to strengthen the NIH AIDS research program.
- o I have established an Office of AIDS Research (OAR) in the Office of the Director to act as the focal point of the NIH AIDS research effort. This office will coordinate the NIH AIDS research program; centralize various AIDS-related policy functions; and represent the Director, NIH, on AIDS-related matters.

- o The Director of the National Institutes of Allergy and Infectious Diseases, Dr. Anthony S. Fauci, will serve as the Associate Director for AIDS Research and lead the Office of AIDS Research.
- o The first meeting of the AIDS Program Advisory Committee was held on February 26, and served to provide an overview of the NIH AIDS research effort. The purpose of this Committee is to advise the Secretary; the Assistant Secretary for Health; the Director, National Institutes of Health; the Associate Director for NIH AIDS Research; and the NIH AIDS Executive Committee on long- and short-term planning to meet research needs in AIDS. Specifically, this Committee will review the overall NIH AIDS research effort to ensure that it is both internally consistent and complementary with efforts taking place in non-Federal research settings. The Committee will also provide advice on policy questions and other matters concerning the NIH AIDS research program.
- o The next meeting of the AIDS Program Advisory Committee, planned for July 12, 1988, will address the topic of HIV vaccine development and testing. Potential topics for future meetings include: the development and testing of antiretroviral therapeutics; basic research related to

AIDS; animal model development; an examination of our efforts in the area of epidemiology and natural history; research on opportunistic diseases; and the AIDS research infrastructure. Specific dates and topics have not yet been selected.

- o I am also pleased to report that NIH has made significant changes in procedures to implement an Accelerated Solicitation Awards Process, (ASAP) for AIDS grants, cooperative agreements, and contracts. To accommodate the February and March 1987 receipt dates additional senior staff from NIH and ADAMHA were assigned temporarily to the Division of Research Grants (DRG) to assist in identifying incoming AIDS applications. This enabled prompt assignments and referrals to appropriate initial review groups and awarding components.
- o This review schedule led to special Council reviews in June, with awards in August. These temporary arrangements are being implemented pending more permanent assignments of additional resources and incorporation of several modifications of current review and award procedures. To further expedite reviews, DRG is in the process of forming a large multidisciplinary

AIDS study section capable of reviewing all facets of basic and applied AIDS research.

- o For award cycles starting in mid-March, repeated announcements will be published in the NIH Guide for Grants and Contracts to inform prospective applicants of the new receipt dates of January 2, May 1, and September 1 of each year. Individual receipt dates for solicited activities will be announced in specific Requests for Applications (RFAs). Similar procedures are planned to expedite evaluation of AIDS contracts.

#### Human Fetal Tissue Transplantation Research

- o This might be a good time, also, to describe briefly our plans for addressing the issue concerning the experimental implant of human fetal cells derived from induced abortions.
- o In FY 1987, the NIH supported 116 grants and contracts involving human fetal tissues at an estimated cost of \$11.2 million. Only one of these research projects utilized human fetal tissue derived from induced abortions for transplantation into humans. That grant was awarded to Dr. Hans Sollinger at the University of Wisconsin, who has performed a total of four human fetal



islet cell transplants. The experimental subjects are still under intensive study.

- o Last fall NIH submitted a request to the Assistant Secretary for Health for approval of a National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) protocol involving transplantation of human fetal tissue derived from induced abortions into the brain of a patient suffering with Parkinson's disease. This protocol would be carried out in the intramural research program at the NIH.
- o The Assistant Secretary for Health responded by requesting that the NIH "convene one or more special outside advisory committees that would examine comprehensively the use of human fetal tissue from induced abortions for transplantation." Dr. Windom also withheld his approval of the "proposed experiment and future experiments in which there is performed transplantation of human tissue from induced abortions" pending the outcome of the outside assessment.
- o While the moratorium on transplantation of human fetal tissue from induced abortions refers only to future research projects and does not apply to research already in progress, Dr. Sollinger and officials at his

institution have reached an independent decision to halt the research pending the recommendations of the outside consultants requested by the Assistant Secretary for Health.

- o Let me emphasize that the restrictions on research do not apply to therapeutic research using human fetal tissue from spontaneous abortions or stillbirths, nor do they apply to nontherapeutic research uses of any legally acquired human fetal tissue.
  
- o To examine the entire issue of experimental implant of fetal tissues derived from induced abortions, I am establishing an Ad Hoc Panel of Consultants to the Advisory Committee to the Director, NIH. Twenty to twenty five individuals will be asked to serve on this panel of consultants. I have asked Judge Arlin Adams to serve as the chairman of this panel. Judge Adams recently retired from the bench on the 3rd Circuit Court of Appeals in Philadelphia. In addition to his excellent judicial and legal reputation, his abiding interest in ethical and medical issues makes him an ideal chairman for this panel of consultants. We are grateful for his willingness to take on this difficult task.

- o NIH has received from many outside sources a substantial number of nominations for the panel of consultants. All nominations have been considered by an internal steering committee, which has recommended to me a balance of ethicists, lawyers, religious leaders, and lay people, as well as scientists and physicians. I will soon be consulting with the chairman to finalize panel membership. Dr. Bernadine Healy will serve as a member of this panel.
  
- o The meeting of the consultants is tentatively scheduled for mid-September and is planned for 3 days in length. The first 2 days will be open to the public and will consist of presentations and discussion from scientific, legal, and ethics experts. In addition, we will advertise in the Federal Register for public testimony from organizations wishing to express views on this issue. Adequate time will be set aside at the meeting to hear this testimony.
  
- o The third day of the meeting will be an executive session for the Panel of Consultants to formulate its answers to the questions from the Assistant Secretary of Health and to draft its final report. We expect to forward the Panel's report, after discussion at our next meeting, to Dr. Windom by late fall.

## OVERVIEW OF REGIONAL MEETINGS

- o As many of you know, at the June 15-16, 1987 meeting of the Advisory Committee to the Director, NIH, we initiated discussion of the health of biomedical research institutions with the aim of examining both the general characteristics and the specific elements of the current Federal system of sponsored research that are contributing to stability or instability of biomedical research institutions and influencing the quality, creativity, and scientific productivity of the biomedical research enterprise. In an effort to extend and intensify those deliberations, a series of regional public meetings were conducted under the auspices of the Advisory Committee to the Director, NIH on that same topic. The meetings were held during the period of November, 1987 to March, 1988 at seven biomedical research institutions located in a range of geographic areas selected to facilitate the participation of representatives from across the entire country. These sites included:

- oo University of California at Los Angeles

- oo University of California, San Francisco



oo New York University

oo Forsyth Dental Center, Boston

oo University of Texas Southwestern Medical Center at  
Dallas

oo Emory University School of Medicine, Atlanta

oo Northwestern University, Chicago

( o I would like to offer my personal expression of appreciation to the faculties and administrations of the just mentioned schools for hosting our meetings and to the members of this Advisory Committee and the representatives of the National Advisory Councils who gave so generously of their time in serving as panel members to receive the public testimony presented at these meetings.

o The purpose of the Regional Meetings was two-fold:

oo First, to provide current information concerning the activities of the NIH by:

- describing the broad political context in which the NIH operates,
  - discussing the Federal budget process as it affects the formulation of the NIH budget
  - demonstrating recent trends in the funding of NIH programs,
  - discussing the broad strategies adopted by NIH to meet emerging needs, and
  - describing new NIH policies and programs designed to achieve program objectives; and
- oo Second, to solicit through public testimony the views of biomedical researchers, university faculty and administrators, representatives of professional societies, and other interested parties concerning the impact of the Federal system of sponsored research on the health of biomedical research institutions.
- o I felt that the first objective--that of informing the scientific community--was necessary since there appeared to be a growing discrepancy between the facts concerning

the policies, programs, and funding of the NIH and the perceptions that have gained currency in the scientific community regarding such factors.

- o I believe that through our opening structured presentations, which you have as part of your briefing materials, we were successful in dispelling some of the myths and misconceptions that may have been clouding perceptions and standing in the way of fruitful discussion so that we were better able to focus our deliberations on the true nature of the problems confronting us.
- o Clearly, however, the major emphasis of these meetings was on the second objective--that of soliciting the views of representative members of the scientific community.
- o As you are aware, the NIH routinely strives to keep the scientific community informed of important new developments and anticipated actions and attempts to involve a broad segment of that community in decisions that have clear implications for universities and other research institutions.

- o We felt that it had become necessary, however, to make a special, concerted effort to renew the dialogue and strengthen communications between the NIH and the constituents it serves, and to involve directly a representative cross-section of that constituency in planning the future course of biomedical research policy.
- o It was toward that end that we devoted the major portion of each meeting to receiving through public testimony the views of representatives of the scientific and academic communities.
- o It was gratifying to note the enthusiasm with which these members of the scientific community and professional organizations accepted my invitation to engage in a frank exchange of views.
- o During the course of the meetings we received testimony from 207 individuals. The first slide indicates the distribution of this testimony among the seven meetings. [SLIDE 1] These public statements were received from a diverse group that included postdoctoral fellows, principal investigators, department chairmen, deans of medical and dental schools, heads of private firms, and



officers and representatives of professional societies and voluntary health organizations.

- o I found these discussions to be especially stimulating, and they provided a wealth of information and suggestions that we will be considering today.
- o A preliminary analysis of the testimony revealed that the views and concerns addressed by the witnesses clustered heavily in about eight major areas. These included: [SLIDE 2]
  - oo **Peer Review**, including a broad array of such sub-issues as (1) the selection and support of truly innovative research, (2) the qualifications and selection of reviewers, (3) the increasing workload of study sections, (4) the excessive amount of time involved in the preparation of grant applications and other administrative burdens associated with the review process, and (5) the meaning and usefulness of priority scores.
  - oo **Flexibility and Continuity of Research Funding**, including questions concerning (1) the feasibility and desirability of providing interim funding pending final determination of a competing renewal

application (2) the use of carryover support through the transfer of unobligated balances for use in a subsequent budget period (3) the adoption of a "sliding scale" to provide partial funding of a larger number of research grants and (4) the provision of longer periods of grant support with a minimum of disruption between grant awards.

- oo Training and Career Development, including the sub-issues of (1) establishing the needs that exist for manpower development (2) the establishment of adequate levels for stipends and (3) the special needs for training of clinical investigators, with much emphasis on Dental Scientist Award.
- oo Research Facilities, including questions concerning (1) specific unmet needs that exist for research facilities and scientific instruments (2) the appropriate role of the Federal government and the private sector in meeting these needs and (3) the potential usefulness of various methods of financing research facilities construction.
- oo Indirect Costs, including the perennial question of how these costs should be apportioned (2) the process of negotiating indirect cost rates (3) the

reasons for the increasing amounts consumed indirect costs and (4) the current practice and future feasibility and desirability of using indirect costs to finance construction of research facilities.

- oo **Research Resources**, including comments concerning support for the Biomedical Research Support Grant Program as a means of meeting institutional needs not served by other mechanisms of research support, (2) opportunities for the conduct of clinical research in settings that provide an interface between basic and clinical research, and (3) access to human cells and tissues for biomedical research.
- oo **Minorities in Biomedical Research**, including (1) views and comments on the success of such current programs as the Minority Biomedical Research Support Program and the Minority Access to Research Careers Program, and (2) suggestions for increasing the number of well-trained minority scientists in biomedical research.
- oo **Animal Research Issues**, including comments and concerns related to (1) the perceived harm to research caused by recent and proposed regulations,

(2) the cost of compliance with increased regulations, and (3) the response of the biomedical research community to animal rights activists.

- o For each of these topic areas I established an NIH Working Group to:
  - oo review relevant testimony on the assigned topic and provide a summary analysis of the views and concerns expressed in that testimony
  - oo identify and describe the salient features of the major issues and concerns within the topic area
  - oo provide, through discussion of pertinent background information, a historical perspective and context to set the stage for discussion of the relevant issues, and
  - oo suggest, where possible, policy options for consideration in responding to suggestions growing out of these regional meetings
- o As you will notice, the reports of these Working Groups form the framework for this meeting.



- oo To further facilitate our deliberations, we have selected individuals to serve as discussants for each of these reports before opening the topic for general discussion by this Committee.
- o In addition to these major clusters of interest and concern, the testimony touched upon a wide range of other topics of special interest to the public witnesses. For instance:
  - oo Several witnesses spoke to the success and importance of the Small Business Innovation Research (SBIR) Program and offered suggestions for further strengthening and increasing the effectiveness of this program.
  - oo Many witnesses urged that increasing emphasis be placed on such specific disciplines, specialties and diseases as organic chemistry, biomedical engineering, radiology, nutrition, transfusion medicine, nursing research, dental research, diabetes, and rehabilitation research.
  - oo Several speakers stressed the important contributions that medical information systems make

to research and medical care and urged the additional investment in medical library systems.

- oo And, a number of witnesses described the special needs and plight of such organizations as small schools and hospital laboratories, private research institutions, and small companies.
- o Against this backdrop I would like to move now to the reports of the chairpersons of the Working Groups, the remarks of the discussants, and general discussion of the issues that have been raised for consideration today.



REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

It is with great pleasure that I bring you sincere congratulations from the National Institutes of Health on this the hundredth anniversary of the opening of the Marine Biological Laboratory. Personally and on behalf of my NIH colleagues I extend warmest wishes to you, Harlyn, as you, the trustees, and your talented colleagues enter a second century of the remarkably productive research for which MBL is known throughout the scientific community.

The events that you have held and that are yet to take place in commemoration of your Centennial are impressive indeed. You have developed a rich schedule of activities appropriate to the MBL and the nature of the anniversary.

My recent experience at the NIH has made me somewhat of a specialist on centennials. Less than six weeks ago we held our final Centennial observance in an extensive series that began in October of 1986. As I have participated in centennial activities I continue to be impressed with the thought that there is something remarkable about the 1880s--the period in history on which observances such as yours and ours have focused attention. It was a time of unusual ferment in the sciences when the ideas of giants, such as Koch, Pasteur, Lister and Darwin, resounded throughout science and stimulated research activity to unprecedented levels. Scientists who understood that they lived in a time of important beginnings took the lead in establishing institutions to foster scientific inquiry. For example, both the National Institutes of Health and the Pasteur Institute were established in 1887. That was also the time when one of our nation's major scientific institutions, the American Physiological Society, had its

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\*Presented at the Marine Biological Laboratory Centennial Celebration in Woods Hole, Massachusetts, July 17, 1988.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



beginning. The Congress passed legislation in 1887 establishing federally supported Agricultural Experiment Stations, the first time substantial Federal support was provided for research of any kind. In the same year the National Association of State Universities and Land Grant Colleges was organized. The concept from which the MBL was formed in 1938 was developed from the same vision, optimism, and confidence that were inspiring the new scientific and academic ventures of the 1880s.

Although there was increasing convergence in the research interests of the MBL and the NIH, it was 50 years before they began collaborative efforts. The earliest grant award to MBL that we can find in our records was made by the National Cancer Institute in 1939, five years before it became a part of the NIH. The award was for \$4,600 and it was made to Paul S. Henshaw. At this time 16 grant awards from 5 institutes are being funded at an annual total of about \$2.25 million.

Earlier I spoke of the excitement and scientific ferment of the 1880s. In many ways the current decade is similar. Giant leaps in the understanding of biology at the molecular level are illustrative of today's accomplishments, and provide the basis for future accomplishment. The bright promise of substantial progress in the neurosciences is of special significance to MBL.

As you enter the second century of the exploration of life by members of your distinguished and unique institution, I am happy to join with your many friends and admirers in wishing you the success you so richly deserve.

REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

I enjoy participating in NIH awards ceremonies. It is a pleasant duty--more a fringe benefit--of the position of Director to be privileged to represent the NIH community in expressing our esteem and gratitude to those of our number who are receiving deserved recognition.

A major aspect of the mission of the Office of the Director is to provide essential support for the programs of the Bureaus, Institutes and Divisions. Consequently, many of today's awards are given in recognition of behind-the-scenes accomplishments. But even though they are not always highly visible, such support activities are no less significant than the better known achievements they have helped to bring about, and in some instances have made possible. Wherever one's assignment may be, each of us needs to remember that what we do, and how we go about it, makes a difference. This is especially true of the personnel of the OD.

Much of what is done in the Office of the Director is at the boundary between the totality of NIH and the rest of the Federal Government, as well as the American people. Our ability to serve effectively depends in part upon the trust and confidence that we have earned among our NIH colleagues as we have worked day by day with them through all seasons. The other component, essential to our effectiveness at the boundary, is determined by the nature and content of our relationships with other parts of the PHS, the DHHS, other Departments, the Congress, the scientific community, the public media and the public at large.

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\*Presented at the OD Honor Awards ceremony,  
Lipsett Auditorium, September 14, 1988.

\*\*Director, National Institutes of Health, Bethesda Maryland.

One of the fundamental responsibilities of the Office of the Director is the nurture and maintenance of the highest standards of excellence in all aspects of our programs. For example, we have given high priority to finding ways for assuring our continued ability to recruit and retain the finest scientists in our intramural research programs.

Obviously, the level of salary we can offer our intramural scientists is high on the list of concerns, and various plans have been put forward to remedy the situation. But such plans do not just "happen." Personnel at many different levels of responsibility and in different offices, such as the Division of Personnel Management and the Division of Financial Management, were involved in the assembly and refinement of the materials that were prepared in support of our case for salary improvement. We can be sure that much more background documentation and justification will be required for each forward step. This kind of work may lack the aura and excitement of involvement in some pioneering laboratory but its outcome may be of more importance to the advancement of science.

Our representations about the need to improve the salaries of scientists reached the White House, and in part were responsible for the issuance of the so-called "privatization" proposal as one means for improving our competitive position.

However, the level of salary is not the only consideration. For many scientists, other, less tangible, negative factors are important--matters such as long delays in providing supplies, and excessive procedural requirements that can frustrate, dampen and retard progress. The Office of Research Services was established to ameliorate some of these problems and 20 of the persons to receive awards are in the ORS.

C. Northcote Parkinson, whose law about mediocrity is well known, commented on government operations by asserting wryly that during World War I, "The British System of accounting was in itself worth an army corps on the other side."<sup>1</sup>

This is not to suggest that accounting should be abolished, but the reference brings to mind an inherent problem in the operation of government agencies, particularly agencies such as the NIH. We have an unquestioned obligation to be fully accountable for public funds. At the same time, our mission requires us to nurture creativity and minimize cumbersome process. Thus the basic operating philosophy of the OD can take us to the borders of comfortable bureaucracy just as B/I/D science can take us to the outer limits of knowledge. Some of us are as challenged to achieve excellence in such matters as designing and using our management data systems as others are to design and carry out fruitful research. It is entirely appropriate that some of our awards today are made for outstanding performance in financial management, personnel administration, and grants management. In different ways each of us is challenged to excellence and creativity, and this pursuit defines the environment of NIH.

In the early 1920s Nobel Laureate Robert Millikan, newly appointed as head of the California Institute of Technology, spoke of the critically important role of such an environment when he advanced the idea that "creative men (and women) arise spontaneously in an atmosphere in which creative men (and women) exist and in general nowhere else."<sup>2</sup>

To all of our awardees, I offer on behalf of their fellow workers, and officially for the NIH, our thanks for jobs well done, and my heartiest congratulations to them, to their friends, and to their families.

#### REFERENCES

<sup>1</sup>Parkinson, C. Northcote, The Law and the Profits, Houghton Mifflin Co., Boston, 1960, p. 133.

<sup>2</sup>Everhart, Thomas E. Inaugural Address as President Cal Tech, summer 1988 issue of Engineering and Science, Pasadena, California, p. 6.





## REMARKS\*

BY

JAMES B. WYNGAARDEN, M.D.\*\*

IT IS MY PLEASURE TO REINFORCE THE WELCOME THAT HAS BEEN EXTENDED TO YOU IN THE EARLIER CEREMONIES, AND TO ADD A SPECIAL WORD OF GREETING AT THIS SYMPOSIUM ON NIEHS RESEARCH HIGHLIGHTS. I SPEAK FOR ALL OF THE NATIONAL INSTITUTES OF HEALTH WHEN I TELL YOU HOW PLEASED AND HONORED WE ARE THAT THIS MEETING OF THE DIRECTORS OF PARTICIPATING INSTITUTIONS OF THE INTERNATIONAL PROGRAM ON CHEMICAL SAFETY IS BEING HELD AT THE HEADQUARTERS OF THE NIEHS.

NIH HAS A LONG HISTORY OF INTERNATIONAL COLLABORATION AND ESPECIALLY WITH THE WORLD HEALTH ORGANIZATION AND I WILL TAKE THIS OPPORTUNITY TO SALUTE WHO ON THE OCCASION OF ITS FORTIETH ANNIVERSARY. THE RESULTS OF WHO'S EFFORTS HAVE BEEN PROFOUND. ENIGMAS OF SCIENCE ARE BEING SOLVED AS RESEARCHERS FROM MANY NATIONS POOL THEIR KNOWLEDGE AND EFFORTS, PROVIDING THE BASIS FOR NEW, APPROPRIATE TECHNOLOGIES FOR DISEASE PREVENTION AND CONTROL. IN ADDITION TO THE OTHER ACTIVITIES IN WHICH WE HAVE JOINED FORCES WITH WHO, CONSTITUENT UNITS OF THE NIH ACT AS COLLABORATING WHO CENTERS IN SIXTEEN DIFFERENT AREAS

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\*PRESENTATION AT THE MEETING OF DIRECTORS OF PARTICIPATING INSTITUTIONS ILO/UNEP/WHO OF THE INTERNATIONAL PROGRAM ON CHEMICAL SAFETY (IPCS), AT NIEHS, RESEARCH TRIANGLE PARK, NORTH CAROLINA, SEPTEMBER 16, 1988.

\*\*DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND.

OF HEALTH-RELATED CONCERNS INCLUDING SUCH TOPICS AS RESEARCH OF THE HEALTH OF THE ELDERLY, DIABETES RESEARCH, INFORMATION AND EDUCATION, APPLIED BIOSAFETY PROGRAMS AND RESEARCH, RESEARCH AND TRAINING IN THE NEUROSCIENCES AND AIDS. AND SINCE 1975 NIEHS HAS BEEN A WHO COLLABORATING HEALTH CENTER FOR ENVIRONMENTAL HEALTH EFFECTS. UNDER THAT PROGRAM ONE OF OUR FUNCTIONS IS TO PROVIDE CONTINUOUS SUPPORT FOR THE IPCS. AMONG NIEHS ACTIVITIES IN THIS CAPACITY HAS BEEN PARTICIPATION IN REVIEW OF THE FORMAT AND CONTENTS OF BRIEF HEALTH AND SAFETY GUIDES FOR ENVIRONMENTAL CHEMICALS, PARTICIPATION IN WORKING GROUPS TO ADVISE WHO AND IPCS ON PRIORITY SETTING OF CHEMICALS FOR HEALTH EVALUATIONS, AND THE PROVISION OF ADVICE AND SCIENTIFIC EXPERTISE TO WHO AND IPCS. THE COLLABORATING CENTER RELATIONSHIPS HAVE PROVIDED THE FRAMEWORK FOR AN EXCHANGE OF SCIENTIFIC INFORMATION ON HEALTH ISSUES AND BIOMEDICAL PROBLEMS OF IMPORTANCE TO BOTH DEVELOPING AND INDUSTRIALIZED COUNTRIES.

THERE HAS BEEN INCREASING CONCERN THROUGHOUT THE WORLD ABOUT THE EXTENT TO WHICH CHEMICALS IN THE ENVIRONMENT MAY CONTRIBUTE TO THE OCCURRENCE OF DISEASE. GROWTH IN INDUSTRIAL AND COMMERCIAL ACTIVITIES, RAPID ACCELERATION OF INDUSTRIALIZATION IN DEVELOPING COUNTRIES, AND HIGHLY PUBLICIZED ACCOUNTS OF CHEMICAL DISASTERS HAVE EXACERBATED THIS CONCERN. IT IS IMPORTANT THAT PROGRAMS SUCH AS THE IPCS CONTINUE TO TAKE A LEADING ROLE IN THE COORDINATION AND DEVELOPMENT OF MULTILATERAL, INTERNATIONAL EFFORTS DEALING WITH ENVIRONMENTAL HEALTH PROBLEMS.

I AM PLEASED THAT NIEHS HAS BEEN A MAJOR PARTICIPANT IN AND SUPPORTER OF THE IPCS. TODAY'S PROGRAM WILL GIVE YOU AN OVERVIEW OF SOME OF THE EXCITING AREAS OF RESEARCH IN ENVIRONMENTAL HEALTH CONDUCTED BY NIEHS RESEARCHERS OR GRANTEES. WE AT NIH BELIEVE IT IS THROUGH EXAMPLES OF SUCH BASIC BIOMEDICAL RESEARCH AS WILL BE DISCUSSED TODAY THAT WE CAN FIND METHODS FOR IMPROVING PUBLIC HEALTH AND FOR INCREASING OUR UNDERSTANDING OF DISEASE PROCESSES. WE ARE DELIGHTED THAT YOU HAVE JOINED US FOR TODAY'S DISCUSSIONS.





REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

The opening of the exhibit on the research of Marshall Nirenberg is a notable event in the history of the DeWitt Stetten, Jr. Museum of Medical Research, and is an impressive reminder of an outstanding moment in the history of the National Institutes of Health. From our current perspective it seems clear that the most significant contribution of the NIH to date is the pioneering work in molecular genetics that began in the 1950s and continues without letup. Marshall Nirenberg had a leading role in this research that has brought about a virtual revolution extending across all of the biological sciences, and the possibilities it unlocked are only beginning to be realized.

Hans Stetten and his advisors rightfully have insisted that highest priority must be given to the development and assembly of the Nirenberg exhibit, and all of us are the richer for their dedication to this task.

For myself, and for all of NIH, I am pleased to express our sincere gratitude to Dr. Stetten, Dr. Harden and their coworkers for their successful efforts. They have created an exhibit that is highly informative and expressive of our pride in the creative work of our colleague and friend Marshall Nirenberg.

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\*Presented at opening of the Nirenberg Exhibit, DeWitt Stetten, Jr. Museum of Medical Research, National Institutes of Health, Bethesda, Maryland, September 20, 1988.

\*\*Director, National Institutes of Health, Bethesda, Maryland



REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

The National Institutes of Health has long been committed to the support of research on the genetics of human development. In Fiscal Year 1987 for example, NIH provided more than \$365 million for the study of genomes of complex organisms, and most of our constituent institutes have been involved in such research. An amount of some \$110 million was specifically focused on the molecular biology of human genetic diseases, although only a fraction of this was used to support the mapping and sequencing of specific genes. Nevertheless, through its several programs in molecular biology the NIH has supplied much of the impetus for the development of new technologies for cloning and purifying DNA, making feasible the mapping and sequencing of the entire human genome.

We now have the necessary tools for initiating a targeted effort that we expect will have a profound and beneficial impact upon our ability to prevent or treat human diseases of known genetic origin, and to understand other disorders having genetic components. For the first time, dedicated funding for the human genome initiative was provided to NIH in the appropriation for Fiscal Year 1988. This amount of \$21 million was increased to \$32 million in the FY 1989 appropriation signed last week by President Reagan. These appropriations also provide for the establishment of a biotechnology information center at the NIH's National Library of Medicine to provide leadership in the development of information handling capability essential to the human genome project. These funds are in addition to the sustained provision for the ongoing research on genetics that is being conducted and supported throughout NIH.

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\*Presented at news conference announcing appointment of Dr. James Watson as Associate Director for Human Genome Research, September 26, 1988.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



As the human genome research project expands and accelerates, other agencies, private organizations, and individual scientists will be involved in it in this country and abroad. But the NIH will continue to have the major role. The time has come for the establishment of an organizational center to direct the NIH human genome project and to coordinate it with other Federal and non-Federal agencies, with industry, and with various national and international scientific organizations.

I am pleased to announce the establishment of the NIH Office of Human Genome Research within the central administration of NIH to carry out the functions that I have just described.

And I am more than delighted to be able to tell you that the new Office will be headed by Nobel Laureate James D. Watson as NIH Associate Director for Human Genome Research. He brings to the position the experience of an unmatched career as a scientist and scientist administrator whose pioneering research in molecular biology has brought him worldwide recognition and respect. He will divide his time between NIH and the Cold Spring Harbor Laboratory that he has headed for 20 years.

I will ask Dr. Watson for whatever remarks he wishes to make at this time, after which we both will be glad to respond to your questions.

It is now my pleasure to introduce the first NIH Associate Director for Human Genome Research, Dr. James D. Watson.

REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

I am privileged and delighted to extend a hearty welcome to all who have come to participate in NIH Research Day '88. In doing so I am mindful of the thanks we owe to the many whose vision and hard work have brought together the wealth of exciting presentations that we will see and hear today. In the time allotted to me it would not be possible to acknowledge the contributions of all who should be mentioned, but I must say a word of special appreciation to Dr. Arthur S. Levine, who chaired the Research Day Organizing Committee and has displayed in his leadership the driving energy for which he is well known. Associated closely with Dr. Levine in this effort were the members of the Organizing and Special Events Committees, whose names are listed on the last page of the program.

The enthusiasm with which so many have agreed to participate in NIH Research Day '88 is clear evidence that it is a good idea to hold such an event. The excitement derives from a general appreciation of the richness of the resources that are brought into being--literally created--through exchanges across the boundaries of the disciplines and subdisciplines of science. Such interchanges take place here every day, informally and often by accident. But today's symposia, poster sessions, and workshops will afford maximal opportunity for members of the NIH scientific community to learn more about each other, and particularly about common scientific interests.

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\*Presented at opening of NIH Research Day '88,  
Bethesda, Maryland, September 27, 1988.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

The range of the topics of the symposia presentations and of the posters is impressive indeed. I suggest that you take the time to read through the program and plan your visits for we have at hand today what can only be described as an embarrassment of riches.

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For Release on Delivery

STATEMENT

BY

JAMES B. WYNGAARDEN, M.D.

DIRECTOR

NATIONAL INSTITUTES OF HEALTH

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

HOUSE GOVERNMENT OPERATIONS SUBCOMMITTEE ON

HUMAN RESOURCES AND INTERGOVERNMENTAL RELATIONS

HOUSE OF REPRESENTATIVES

SEPTEMBER 29, 1988



Mr. Chairman and Members of the Subcommittee:

This morning I have been asked to address recent efforts made by the NIH in dealing with allegations of misconduct in science since the hearing by this Committee on April 11, 1988. With me are Dr. Katherine L. Bick, Deputy Director for Extramural Research, and Dr. Charles R. McCarthy, Director, Office for Protection from Research Risks. I am pleased to report that we have taken a number of steps to strengthen NIH responsiveness to allegations of possible misconduct in science. I would also like to describe some of the forward looking efforts now underway that bear directly on the progress NIH is making in promoting responsible conduct of biomedical science.

The NIH is deeply committed to maintaining the integrity of the scientific research enterprise supported by public funds. Misconduct and dishonest behavior in science are so serious and so undermine the creation of a sound knowledge base in biomedical science that they are of great concern to all--the scientific community, the NIH as the principal Federal agency for support and conduct of biomedical research, Congress, and the American public.

Misconduct in science is currently defined by the Public Health Service (PHS) as (1) fabrication, falsification, or plagiarism from accepted practices in carrying out research or in reporting the results of research; or (2) material failure to comply with Federal requirements affecting specific aspects of the conduct of research, e.g., the protection of human

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subjects and the welfare of laboratory animals. This definition is directed at all dishonest practices that undermine scientific integrity.

Policies and procedures to address allegations of misconduct in science have been formulated and are described in the NIH Guide for Grants and Contracts, Vol. 15, No 11, July 18, 1986. Accumulation of case experience and resolution of unusual issues have provided an informative basis for application of these procedures.

Since 1982, the Institutional Liaison Office, Office of Extramural Research, Office of the Director, NIH, has dealt with approximately 15 to 20 allegations per year of possible misconduct in science. The topics of alleged wrongdoing in our files range from deliberately deceptive or fraudulent practices such as fabrication and falsification of data, to making an honest error in judgment or in practice, to scientific disputes about the interpretation of data. As we go through the stages of inquiry, we may find a vendetta, a purely scientific dispute, "sloppy science," or outright wrongdoing. Quite often there is a mix.

Three-quarters of the incidents in our file are closed cases. Of these, in more than 50 percent of the allegations of misconduct, there was no evidence to support the charge. We are currently working on approximately 25 open cases in various stages of inquiry or investigation. Most of these were brought to our attention within the last two years. The NIH has taken a number of steps recently to improve responsiveness to instances of alleged misconduct.

### Increased Staffing

Two professionals have been added to the office that handles the allegations of misconduct in science, the Institutional Liaison Office. This increases the core staff to five full time equivalent positions. These additional staff members will not only help to improve the NIH response time in handling cases under review, they will also enable us to identify and analyze aspects of the various cases, so that we can learn from them and refine and improve NIH policies.

Two investigators are being added to our internal audit branch staff, the Division of Management Survey and Review (DMSR). DMSR staff serve the NIH on audit matters involving misuse of Federal government funds or property. These individuals work closely with staff in the Institutional Liaison Office on selected investigations of possible misconduct in science depending on the nature of the problems being addressed. An additional professional will join the Office of the NIH Legal Advisor. Among their other assignments, these individuals will assist in casework on allegations of misconduct in science. Our goal is to have no backlog of cases.

I might add that several of my senior staff including Dr. Raub, the Deputy Director, Dr. Bick, Mr. Robert Lanman, the NIH Legal Advisor, and Dr. George Galasso, Associate Director for Extramural Affairs, also devote a great deal of attention to the issues and concerns involving misconduct in science. We are also developing ways to expand on our existing practice of seeking assistance from scientists at NIH and elsewhere in the evaluation and investigation of allegations.

### Improved Communication

CASETRAC Database System. To increase our analytical capabilities, a computerized system for tracking responses from the institutions conducting inquiries on complaints and allegations of misconduct and fraud has been developed and is now operating. This system enables the NIH to control information and monitor progress on the case from the time an allegation is received to the time when the case is closed. The system will help produce a number of status and summary reports to facilitate handling inquiries and investigations of misconduct in science.

ALERT System. The NIH ALERT system serves all PHS agencies. The ALERT is a system of records that includes the information on individuals under investigation for possible misconduct in science or persons who have had sanctions imposed on them for misconduct in science. Controlled disclosure is made, as appropriate, to other PHS components because the subjects of investigations or sanctions of one PHS component may receive or be candidates for research and development awards from other PHS agencies or offices.

Education. We have concentrated on several efforts to update the NIH scientific community on issues and concerns in misconduct in science. Just yesterday, the continuing education program for the NIH staff held the first of two formal training sessions for the NIH. A forum on the Misconduct in Science apprised the staff on current PHS and DHHS initiatives and re-emphasized the responsibilities of NIH extramural staff members.



In January, an intensive two-day program will examine issues that affect the integrity of science, both within and outside the NIH. This training module will include a substantive review of issues with faculty members from various professional fields--ethics, law, science publication--and different scientific disciplines knowledgeable about the prevention of misconduct in science or with involvement in handling allegations of possible misconduct. Also planned is mandatory training for all staff whose responsibilities include scientific program management and administration of grants and contracts.

PHS Committee on Misconduct in Science. The PHS Committee on Misconduct in Science meets regularly to discuss the common problems faced and issues to be resolved in each of the PHS agencies. Among these are (1) time frames and deadlines for action on misconduct cases; (2) consistency in application of debarment and suspension procedures; (3) due process and appeals; (4) responsibilities for correcting the scientific literature; and (5) practices for recording and retention of research data.

#### NIH Project Initiatives

Institution Case Study. To document and clarify the nature of the problems of misconduct in science and how institutions handle accusations, we intend to conduct an evaluation study of the strengths and weaknesses of various approaches used by the universities to investigate allegations of research improprieties. The focus of the study is on the lessons learned in carrying out the practical aspects and logistics of the investigation. This study will allow us to (1) identify the more common administrative problems

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encountered in conducting the investigations from detection and allegation to suspension or exoneration; (2) ascertain how goals were set to organize the logistics of conducting the investigations; and (3) organize the information obtained to share with individuals and institutions having similar concerns.

The level of university resource investment required, what approaches work best given the different situations and types of misconduct, and the information flow within the institution are also of interest. The project goal is to increase the effectiveness of the NIH in providing guidance to, and assessing the performance of, the institutions.

Institute of Medicine Study. In October, 1987, the NIH contracted with the Institute of Medicine (IOM) to conduct a study to develop principles and procedures to address the promotion of scientific responsibility and quality assurance in research. As part of this study, the IOM recently convened a workshop on "Responsible Conduct of Research in the Health Sciences" (September 6-8, 1988) to enable about 100 scientists, government and university officials, representatives of professional societies, and journal editors to share their views on the ways to assure integrity and quality in research.

Topics discussed by the Committee and workshop participants included: (1) laboratory practices and standards; (2) clinical research practices and standards; (3) issues in institutional oversight; (4) education and training for research; (5) academic and career advancement; and (6) authorship,

referee, and publication standards. The need for preventive measures was emphasized. The participants agreed that scientific quality and integrity in research can be advanced by developing specific guidelines and recommendations for many of the practices included under these topics. Through the IOM study, the NIH seeks to develop recommendations on the best approaches to promote scientific integrity in the conduct of biomedical research. The IOM report is expected to be submitted to the NIH in January, 1989.

Commissioned Paper for National Conference of Lawyers and Scientists (NCLS). The NIH sponsored a commissioned paper, "Whistleblowing in Academic Research," for the NCLS workshop held on September 23-25, 1988. This paper addressed the points of legal protection in whistleblowing; effects of university misconduct policies on whistleblowers; and assessing the veracity of whistleblowers' claims.

#### DHHS Initiatives

Office of Inspector General (OIG) Report. We have had an opportunity to review a draft of the report, "Misconduct in Scientific Research: Activities of NIH Grantees." We note that the findings of the OIG inspection of activities of NIH grantee institutions ascertained that 93% of NIH awardee institutions with 100 or more awards have policies and procedures in place to deal with possible misconduct in science.

The OIG report provides us with some of the groundwork for the NIH Project Initiative, the Institution Case Study, to which I referred earlier. We

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intend to carry out a more systematic follow-up on several of the indicated results.

Notice of Proposed Rulemaking (NPRM) / Advance Notice of Proposed Rulemaking (ANPRM). Section 493 of the Public Health Service Act contemplates that there will be a close working relationship between the NIH and the awardee institutions in resolving allegations of scientific misconduct. Section 493 envisions that the primary responsibility for the resolution of allegations of misconduct in science rests with the awardee institutions, but NIH retains the responsibility and authority for monitoring the investigations and becoming involved in them at the appropriate time. The NPRM outlines the basic responsibilities of the institutions and provides an opportunity for comment by institutions, scientists, and other members of the public.

The ANPRM requests public comment on a number of options the Department is considering for defining in greater detail the scope and nature of the Departmental and institutional responsibilities for preventing, detecting, and resolving instances of misconduct in science. We will be developing such further comprehensive regulations as may be necessary taking into account the public comments made on the ANPRM.

#### Conclusion

We are extremely sensitive to the NIH role in prevention and detection of research fraud and misconduct. We are making more explicit the procedures that are necessary to deal with misconduct in science and to develop ways to promote the prevention of deviant behavior in the conduct of biomedical



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science. There is strong interest in applying the range of tested and successful policies that the Federal government and the research institutions have in place to respond to allegations of fraud and misconduct.

We are confident that the collective experience of the research community and the PHS funding agencies will facilitate and further shape guidelines and criteria for fraud and misconduct investigations. A continuing challenge will be to avoid intrusion upon the traditional scientific autonomy required by productive and creative scientists while attempting to formalize the institutional obligations for quality assurance and accountability.

I hope this brief document outlines the progress we are making. We welcome the interest of the Congress and look forward to continued progress in meeting the challenge that misconduct in science presents to the biomedical research community.

REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

There are critical times in the history of most enduring institutions when their future course is in large measure determined by the vision and force of an individual leader. It was vital to the future of the National Institutes of Health in its period of formative growth that there be a farsighted leader such as James Shannon, who understood that eventual success in the conquest of disease depended first upon a great expansion of knowledge of biological systems, on an army of well trained scientists, and on a strengthening of the institutions where the bulk of research and training would be done.

It is one thing to have such understanding but of equal if not greater importance to act upon it. And Jim Shannon is a man of action. His eminently productive association with NIH began when he could not resist the opportunity he was offered to organize and operate, from scratch, the intramural research program of the newly-created National Heart Institute. It was a substantial task for 1949, or any other time, for it entailed the recruitment of about 100 scientists, and installing them in some 350 laboratory modules with adequate technical and administrative support. It looked forward to the operation of about 100 research beds and their necessary laboratory, nursing and social service backup.

He was able to recruit a young and talented cadre of investigators to the Heart Institute, including such promising leaders as Chris Anfinsen, Bernard Brodie, Sid Udenfriend, and Julius Axelrod. There are many more whose names would be known to this audience. While the recruitment for people below the level of heads of laboratories or branches was delegated,

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\*Presented at FASEB ceremony honoring Dr. James A. Shannon, September 30, 1988.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

for the most part to the chiefs of these units, Jim personally developed the training program for aspirant physician-scientists and hired the first cohort--called clinical and research associates. Don Fredrickson and I were in this group. The Heart Institute's intramural program was the first of Shannon's memorable contributions to the NIH.

When he became Director of NIH in 1955 the intramural programs of all components were in a period of rapid growth. The Clinical Center had been opened in 1953 and the staffing of the intramural laboratories for both basic and clinical research was proceeding.

As he planned for the years ahead and gave attention to the extramural programs of NIH, it became clear to him that existing institutional facilities and personnel resources at grantee institutions would not suffice. He strongly advocated and nurtured programs for the construction of research facilities in academic centers. He also saw the critical need for biomedical research training programs within existing medical centers and graduate schools.

Jim Shannon showed unusual political skill in dealing with members of the Congress. He understood their interests and concerns, and was able to convince key members that if we were to succeed in making substantial progress against disease and disability we must build upon an ever growing fund of basic knowledge. The high regard in which he was held by such leaders as John Fogarty and Lister Hill was a source of great strength for NIH. Certainly these relationships played a significant role in sustaining the phenomenal growth in the NIH budget from \$82 million in 1955 to \$1.2 billion in 1968, an average increase of 24 percent per year.

An indirect achievement of the NIH, much of which is attributable to Jim Shannon, is the transformation that the agency's programs brought about in American universities. Their cumulative effect has been especially marked in the area of the biological sciences. This came about in large part through the infusion of scientists trained in the intramural programs of the NIH in both basic and clinical research. Bethesda-trained investigators have seeded preclinical and clinical departments of medical schools

and bioscience departments in universities across the breadth of the land. The NIH influence has also been exerted through rapidly increasing levels of support of research, of training, and of facilities, and especially through the additions such funding made possible in increasing the numbers of faculty oriented toward research.

A simple explanation of our honoree's remarkable achievements was suggested in a presentation given at New York University last year by Tom Kennedy, who was a longtime member of the Shannon team. Commenting on Jim's approach to his newly assumed responsibilities as NIH Director, Tom noted that, "In his new role, he continued to display his extraordinary nose for talent, to insist on demanding standards of performance, and to create an aura of excellence." These qualities continue to guide and challenge all who have positions of responsibility at NIH.

As one who has given constant and careful study not only to the objectives of the NIH, but particularly to the means for carrying out its truly noble mission, I have encountered repeatedly examples of his inventive approach to the subtleties of management of a large scientific enterprise. By the time of his retirement in 1968 most of the current organizational structure of the NIH was in place. And so, in addition to my personal admiration and affection for Jim Shannon over a period of nearly 40 years, I have gained during the past 6 years a special appreciation for the vision, ingenuity, and good judgement with which Jim shaped and nurtured the NIH into a unique and powerful instrument to serve the needs and highest aspirations of humanity.





## INTRODUCTORY REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

We are delighted that Dr. Thomas R. Cech is with us today to present the NIH Lecture. Dr. Cech is a distinguished and innovative scientist. His contributions to an increased understanding of RNA are setting a scientific agenda for important research. His discovery that RNA can function as an enzyme and assemble itself overturned previously held ideas.

Dr. Cech was intrigued when he learned that several researchers had found evidence that RNA-protetin complexes of some microorganisms had enzymatic properties. Following this lead, in 1982, he and his colleagues detected enzymatic activity in a supposedly pure sample of ribosomal RNA from the protozoan Tetrahymena. Thinking at first there was some other explanation they then became convinced that precursor ribosomal RNA was capable of transforming itself into mature RNA through "self-splicing," cleavage followed by ligation--in the absence of any protein enzyme.

Dr. Cech and his colleagues have demonstrated that RNA acts as a true enzyme. These findings, supported as they have been with extensive classical chemical and biochemical methodology, are nothing less than landmark advances in understanding the role of RNA in cell activity. No longer can one assume that protein lies behind every catalytic activity of a cell.

Dr. Cech's discovery that RNA can act on its own as both an information carrying molecule and an enzyme speaks to the basic questions of the origins of life. The capacity of RNA to function without DNA or protein, has implications for evolution that have been both embraced and challenged by evolutionary biologists. It may be that Dr. Cech's work will help to answer the biological version of which came first, the "chicken or the egg" and to give RNA first place over DNA or protein.

Dr. Cech received his Ph.D. in chemistry at the University of California, Berkeley, in 1975 and was a postdoctoral fellow in the biology department of the Massachusetts Institute of Technology in Boston. He is a joint professor of chemistry and biochemistry, and molecular, cellular, and developmental biology at the University of Colorado and an investigator at the Howard Hughes Medical Institute. An American Cancer Society research professor, he recently received the Heinëken Award from the Royal Netherlands Academy of Science. Dr. Cech has held a National Cancer Institute Career Development Award and is a member of the National Academy of Sciences.

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\*For NIH Lecturer, Dr. Thomas R. Cech, at the Clinical Center on November 2, 1988.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

Today he joins an illustrious group who have given the NIH lectures since they began in 1953 and honors us by being here. The title of Dr. Cech's presentation is "RNA as an Enzyme."

Dr. Cech,

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THE HEALTH OF BIOMEDICAL RESEARCH IN THE UNITED STATES\*

by

James B. Wyngaarden, M.D.\*\*

It is a special honor to have been asked to deliver the John and Margaret Cochrane Lecture. I regret that Mr. and Mrs. Cochrane are not with us today, for I would have liked to add my words of appreciation to them for the major role they played in establishing the research chair honoring the late Professor Holley, the chair to which Bill Koopman has been appointed as the Howard L. Holley Professor of Medicine.

In my lecture I will address the subject of "The Health of Biomedical Research in the United States." My observations will be made from the perspective of the National Institutes of Health, and in the main will concern issues and opportunities that currently challenge that institution. The NIH is a good vantage point because it is the largest single entity in the nation devoted to biomedical research. In its extramural programs it is involved in close and continuing collaboration with practically all of the biomedical research institutions in the nation, and through them with some 50,000 research scientists.

The topics I plan to discuss include: the growing influence of industry as a partner in biomedical research; biotechnology; the NIH initiative in human genome research; the status of the massive research effort against AIDS; concerns about the continuing need for trained scientists; and some general observations about issues affecting all of the biomedical research community.

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\*Presented as the Fifth John and Margaret Cochrane Lecture,  
University of Alabama at Birmingham, Birmingham, Alabama,  
November 17, 1988.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



## FROM A TWO-WAY TO A THREE-WAY PARTNERSHIP

For the past 40 years NIH research activities have been carried out in large part through a two-way partnership between the Federal Government on the one hand and academic institutions, hospitals, and nonprofit laboratories on the other. In recent years a third category of partners has joined the national biomedical research endeavor, so that now industry, academia and the Government work closely in mutually supportive efforts to combat the age old problems of disease, disability, and premature death.

Concurrently with the evolution of new and productive modes of collaboration between industry and academic institutions, industry's share of the total national investment in biomedical research has been growing rapidly. As recently as 1981 the total spent by all of American industry for health-related research and development was less than the research budget of NIH alone. In 1982 NIH's share of the nation's total expenditures for health-related research and development was 37 percent, and that year it was for the first time matched by industry, and in the subsequent years the industrial component has more than kept pace. By 1987 industry was spending about \$6.8 billion annually for health research and development, while the NIH's research expenditures came to a total of \$5.5 billion. Thus, in 1987 industry provided 42 percent of the national total as compared with 34 percent from NIH. Direct collaboration between industry and NIH is only now beginning to expand.

The Federal Technology Transfer Act of 1986 provides incentives that are stimulating accelerated interest in formal collaboration between government laboratories and industry. The intent of Congress in passing the Technology Transfer Act was to assure that the results of government-conducted research become available commercially through patenting and licensing of inventions, thereby contributing to America's competitiveness in the world marketplace.

Although the full impact of the Technology Transfer Act will not be felt for some time, NIH already is experiencing accelerated activity in the area of invention development and biotechnology transfer. There is an

increasing interest by companies in negotiating cooperative R & D agreements with NIH scientists, and although in 1987 income from NIH inventions amounted to well under one percent of our intramural budget, the fees and royalties are on the increase.

Such benefits must be viewed in perspective however, because the NIH is primarily involved in the long-term pursuit of basic knowledge about life processes and disease, in which most discoveries are made well in advance of the possibility of commercial application. The NIH intramural program is a national resource of scientists and facilities in large part devoted to the important tasks of basic research, and obviously it is our intention to continue to serve this mission while facilitating the transfer of such findings as are applicable to practical usefulness. We are sensitive to the possible negative effects of too great an emphasis in our programs on applied research and development. This can divert us from our most important pursuit.

Yet, as a result of significant gains in understanding the basic processes of life, biotechnology has emerged as a major new economic force in the world, and it offers great promise of benefit.

The prime examples of biotechnology stem from recombinant DNA. Investigators have been conducting research with this new technique since the 1970s. In the beginning, concerns were raised in the scientific community regarding the potential risks of applying this powerful new tool without adequate information to ensure the safety of the general population and those involved with the technology. The NIH took the lead in developing and continuously updating guidelines to cover research with recombinant DNA, but they were never intended to cover development and commercialization of genetically engineered organisms. Other Federal agencies have jurisdiction over these areas. To provide a forum for interagency coordination on such matters, the Biotechnology Science Coordinating Committee was chartered. It reports to the President's science advisor and consists of representatives from EPA, USDA, NSF, FDA, and NIH. I currently am chairman of the committee.

Internationally the Organization for Economic Cooperation and Development provides an informal forum for coordination of the application of regulations to biotechnology. Through it we hope to avoid major differences in the application of guidelines among participating nations; to share experiences and to avoid unnecessarily restraining development through an excess of caution leading us to tie our own hands.

The NIH has a serious commitment to maintaining the science base necessary to fuel further advances in biotechnology. This will be carried out through the support of research on fundamental biological processes and the training of future generations of molecular biologists. By virtue of its expertise in these areas, NIH also will continue to participate in efforts to understand the effects of the applications of genetic engineering techniques to ensure their safe and productive use.

#### THE HUMAN GENOME PROJECT

The NIH has been the major player in the development of genetic information and in genetic research for the past several decades. In Fiscal Year 1987, NIH provided more than \$365 million for the study of the molecular biology of complex organisms, and most of our constituent institutes have been involved in such research. An amount of \$110 million was focused specifically on the molecular biology of human genetic diseases, although only a fraction of this amount was used to support the mapping and sequencing of specific genes. Nevertheless, through its several programs in molecular biology, the NIH has supplied much of the impetus for the development of new techniques for cloning and purifying DNA, making feasible the human genome project.

In FY 1988, NIH received \$17.3 million in new funding for a new research program to map and sequence complex genomes. The President's budget request for FY 1989 increased that amount to \$28 million. These funds will be used to support a scientific approach that is very different from existing work on complex genomes. The new program and the dedicated funds will seek to locate genetic markers that are increasingly shorter

distances apart along the entire stretch of chromosomes, and ultimately to define the structure at the level of the individual nucleotide sequences.

In recognition of the high priority placed on mapping and sequencing the human genome and the overarching planning and resource demands of a systematic targeted effort, a new Office of Human Genome Research has been established within the Office of the Director, NIH, and will be headed by Nobelist James D. Watson as the Associate Director for Human Genome Research. The function of the office is to provide coordination, integration, review of progress, and planning in genomic analysis research. Research goals and long-range plans will be formulated with the guidance of a newly-chartered NIH Program Advisory Committee on the Human Genome and the NIH Working Group on the Human Genome. This strategy permits centralized coordination of the trans-NIH effort while maintaining the elements of peer review and program planning that are essential to a successful research initiative.

One of the key responsibilities of the new office will be to coordinate the NIH planning process with the other Federal agencies and research funding institutions involved. The NIH provides the lion's share of the Federal investment in genomic analysis. However, the Department of Energy and the National Science Foundation have a history of supporting research programs that are relevant to the genome project. There are already a number of joint projects under way that contribute to a national effort. At the working level, scientists funded by all three agencies collaborate on a number of investigations.

#### AIDS RESEARCH

The urgency and level of scientific, public, and political concern over the AIDS epidemic are manifest in one of the largest and most intensive research efforts ever mounted. It resembles in a number of ways the launching of the war on cancer in the early 1970s. As in the earlier instance, the NIH is committed to providing the leadership and direction necessary to marshal the resources and talents of the biomedical research community to combat this disease. The NIH is making every effort to ensure that AIDS funding is deployed in the most effective manner possible and



that AIDS research proceeds expeditiously. We have established an Office of AIDS Research within the Office of the Director that will act as a focal point for AIDS research. The purpose of the office is to coordinate the NIH AIDS research program, centralize various AIDS-related policy and operating functions, and represent the NIH Director on AIDS-related matters.

The Director of the National Institute of Allergy and Infectious Diseases, Dr. Anthony S. Fauci, now serves in a dual role as Associate Director for AIDS Research, and heads the new office. Dr. Fauci has functioned as NIH AIDS coordinator since 1985. At that time our AIDS research activities were concentrated largely in three institutes, but since then an almost tenfold expansion of AIDS efforts has occurred. The current annual budget is \$607 million and essentially all components of NIH are now involved. Another important resource in the NIH AIDS management structure will provide advice from the non-Federal research community and the public. An AIDS Program Advisory Committee was chartered last year. Its membership includes nine scientists and four nonscientists, and its function is to provide advice on overall AIDS-related research directions, scientific opportunities, policy questions, and major program initiatives to be undertaken by the NIH.

#### A CONTINUING SUPPLY OF TRAINED SCIENTISTS

To maintain the pace of scientific advances, and particularly to press forward in carrying out initiatives such as biotechnology, the human genome project, and the great expansion of AIDS research, we must ensure that there is a continuing supply of bright and well-trained scientists. The Government-University-Industry Research Round Table of the National Academy of Sciences has been exploring issues relating to the identification, recruitment, development, and retention of science and engineering talent. In evaluating the talent pool, the round table group predicts that demand for scientists and engineers will remain strong in both industry and academia, but that at the same time the numbers of Americans in the age groups that normally would be expected to be in training for these careers will be declining. For example, the current number of 22-year-olds is projected to drop more than 25 percent before the end of this century.

Even if the current number were not to decline, a significant increase in the proportion of 22-year-olds attaining scientific and engineering degrees would be required to meet the projected research needs. In fact, the Round Table group estimated that to maintain the 1985 level of potential research trainees into the 1990's the degree award rate would have to increase by 30 percent. Unfortunately the number of baccalaureate degrees awarded in the life sciences has decreased steadily since 1977 to the present.

The number of full-time graduate students in the biological sciences has risen by about 1,000 during each of the past two years, after a six-year period of little or no change, but foreign students accounted for most of the increase. In 1987 there were about 38,000 such graduate students in the biological sciences and about one-fourth of them were foreign nationals. There have also been steady increases in the number of postdoctorates and other nonfaculty research staff in the biological sciences since 1980. Also, the number of women in graduate programs and postgraduate non-faculty staffs in the biological sciences has increased. Among the graduate students in 1980 only 7 percent were women--by 1987 that ratio had risen to 42 percent. Among the postdoctorates the proportion who are women increased from 25 percent in 1980 to 32 percent in 1987.

The proportion of underrepresented minorities among graduate students who are U.S. citizens is 5.4 percent. The minority representation is low, but reflects a continuing improvement since 1981 when it was only 3.7 percent. However, the message is clear. If we are to realize the promises implicit in the recent and rapid gains in the biosciences, we must attract greater numbers from a diminishing age group of our population. It is encouraging that there has been some progress in the past few years.

The interdependence of training and research has become increasingly apparent as the size and scope of the biomedical research enterprise has increased. This linkage provides the opportunity for the development of the next generation of scientists in the same laboratories where new discoveries are now being made. The National Research Service Awards and Research Career Programs of NIH serve several functions: They attract students to research careers; they enhance research environments; and most

of all, they help to ensure the future progress of the nation's research enterprise by maintaining a flow of well-trained young scientists into research careers.

#### SOME MATTERS OF GENERAL INTEREST

Since I am reporting on the current status of the NIH, I must tell you of the authorization by an Act of Congress, signed on October 29, of a new National Institute on Deafness and Other Communication Disorders (NIDCD). In keeping with the pattern that has developed in recent years, the new institute, NIH's thirteenth, will be created by transfer of a portion of the appropriation and program of an existing institute. The NIDCD has been appropriated up to \$96.1 million for the current year which will be transferred from the National Institute of Neurological and Communicative Disorders and Stroke. The purposes of the institute parallel those of the existing institutes, and include the conduct and support of research and training, dissemination of health information and other programs with respect to disorders of hearing and other communication processes.

In my remaining time I will discuss two matters of general concern that have been receiving considerable attention in the national media. One is the escalating controversy between the biomedical research community and animal welfare advocates concerning the use of animals in research. Federally supported laboratories have been the targets of illegal break-ins; theft of animals; and destruction of property, equipment, and valuable records. The NIH has been the site of a sit-in, prolonged picketing, and two recent demonstrations by animal rights activists.

Vertebrate animals, especially mammals, are critical to progress in many avenues of biomedical research. In using them as subjects of biomedical research, we must recognize the responsibility associated with such use. This responsibility requires the appropriate employment of animals in biomedical research while making every effort to provide humane care and an optimal environment for the animals.

Together with academia, industry, and other government agencies NIH strives to ensure the humane care of research animals, to educate the public and Congress about the facts relating to the use of animals in research, and to explain the need for, as well as the benefits of, animal research in understanding and treating human disease and improving animal welfare.

Although animals are essential for advance of knowledge in the biomedical sciences, NIH recognizes that nonanimal research methods provide additional opportunities to advance understanding of biological processes. Applications are continually being sought for proposals to develop methods that do not require vertebrate animals, that reduce the number of vertebrate animals used, that produce less pain and distress than current procedures, that validate reliability of nonanimal methods, and that develop other methods found valid such as physical and mathematical models.

The introduction of legislation concerning various aspects of animal welfare is increasingly common in Congress and in state legislatures. Twelve states, including Maryland, have enacted legislation prohibiting the release of shelter/pound animals for research use. The NIH position on the use of pound animals is basically that animals selected for research projects must be of an appropriate species, number and quality--that decisions as to the kinds and sources of animals that are most appropriate for particular studies must be made by the scientists who define the purpose for which the animals are required. The NIH neither specifies nor proscribes the sources of animals to be used in the biomedical research projects which it supports or conducts.

Eleven bills on different aspects of the care and use of animals were introduced in the 100th Congress. While we are in agreement with the intent of several of these bills, some of them could have severely hindered NIH-funded biomedical research efforts if enacted as proposed. We believe that by working closely on these matters with Congress and other government agencies, it will be possible for the NIH to continue to serve both the public need for better health and the public desire for the appropriate care and use of animals in biomedical research.



The second general topic I will discuss briefly is the issue of misconduct in science. Although I personally believe that biomedical scientists equal or surpass any other professional group for integrity, and high purpose, one must admit that recent substantial examples of dishonesty have severely damaged public confidence in our enterprise. The NIH, the scientific community, and the academic and professional institutions are deeply committed to maintaining the integrity of the scientific research process. Misconduct and dishonest behavior in science, though infrequent, are so serious and undermining to the creation of a sound knowledge base in biomedical science that it is of great concern to all participants in research, as well as to the American public. It is our policy that grantee and contractor institutions receiving NIH research support have the primary responsibility for dealing with possible misconduct involving their scientists. This responsibility includes the duty to conduct inquiries or investigations as appropriate, and to inform and cooperate with NIH as the funding agency. It is not known whether the incidence rate of misconduct in science itself has risen within the past decade or so, but it is clear that the number of reports of misconduct have increased, requiring NIH to make more explicit the procedures to deal with this phenomenon and to develop ways to prevent such behavior.

Since 1982 NIH has dealt with approximately 100 cases. In these, the alleged wrongdoing ranged from deliberately deceptive or fraudulent practices, such as fabrication and falsification of data, to honest errors in judgment or practice, or in some instances scientific disputes.

Grantee institutions have been expanding their efforts during the past several years to monitor, investigate, and report research misconduct involving Federal funds, and to promote quality assurance and accountability in the conduct of science. However, there is still a far too prevalent reluctance on the part of universities and other grantee institutions to engage this unpalatable issue. Recent history shows that unless an institution has a well planned mechanism in place, they will surely mess up when their first misconduct or fraud case occurs. There is also a continuing challenge to avoid intrusion upon the traditional scientific autonomy

required by productive and creative scientists while attempting to formalize the institutional obligations for quality assurance or accountability.

For its part, and to provide a more efficient operation, the NIH has increased core staff within the Office of Extramural Research to improve response time in handling cases under review, provide more extensive liaison with the research institutions conducting NIH-sponsored research, and facilitate ways to gather data and seek guidance from the extramural scientific community and from within the NIH scientific community. In the context of the heightened sensitivity to the imperative of preventing and detecting research fraud and misconduct, the collective experience of NIH and institutions in promoting scientific responsibility and conducting inquiries provides an optimum vantage point for policy formulation and implementation of mechanisms to facilitate and shape guidelines for fraud and misconduct investigations.

On September 19, Notices of Proposed Rulemaking were published in the FEDERAL REGISTER by DHHS and NIH on the responsibilities of awardee and applicant institutions for dealing with possible misconduct in science and the development of protective regulations. Public comments were requested on issues raised by the proposed regulations, such as the organizational location of the Office of Scientific Integrity and the need to be certain that strong scientific review is the first component of any inquiry. It is essential in dealing with these matters that our efforts to remedy current problems not lead to the development of a vigilante or "ethics cop" mentality with such actions as random, unannounced site visits and data notebook reviews.

Because there may be other topics related to the health of the biomedical research enterprise in which you have interest and that I have not addressed, I have saved some of my allotted time for your questions or comments, to which I would be glad to respond.



# STRATEGIC PLANNING FOR RESEARCH IN THE MEDICAL SCIENCES

by

James B. Wyngaarden, M.D.\*\*

The pace of biomedical research has increased markedly in the past several years, and there has been a change in its character. The most prominent qualitative change has been the maturation of molecular biology with the resultant emergence of biotechnology-based agents and procedures for diagnosis and treatment of disease. The pace continues to increase as medical scientists progressively shorten the time between discovery and application. Thus, accurate projections of the nature and effects of these discoveries are difficult, even for the next five years, much less into the next century. In his apt way, Lewis Thomas stated the problem of making such forecasts. "It is hard," he said, "to predict how science is going to turn out, and if it is really good science, it is impossible to predict. This is the nature of the enterprise."<sup>1</sup> The difficulty, however, does not diminish our shared responsibility for planning what can be planned to make it possible to continue--or even to accelerate--the progress of medical science. It is helpful that some general areas of future progress seem clear and that useful predictions can be made.

For example, I feel secure in projecting future activities on the assumption that the current approach of the Federal Government to fostering biomedical research will serve the nation well for the foreseeable future. The NIH supports and conducts research across the spectrum from basic science to targeted projects, with special emphasis on learning more about the fundamental life processes at the cellular and molecular levels.

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\*Presented at the Medical Alumni Weekend Scientific Program,  
Duke University Medical Center, Durham, North Carolina,  
November 18, 1988.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



Our objectives are pursued through many pathways, including intramural laboratories and clinics, those of academic health centers and other institutions of higher education, private sector pharmaceutical and biotechnical companies, and a host of other not-for-profit as well as commercial organizations. Although the relative emphases among objectives and strategies will undoubtedly change from time to time, the current model should serve effectively far into the next century.

In addressing the subject of "Strategic Planning for Research in the Medical Sciences," the dissonance between the words "research" and "planning" is resolved when it is clear that we are speaking of strategic planning "for" and not the planning "of" research. In fact, the need to plan for research has become ever more pressing as the activity has become more expensive and sophisticated. Dan Greenberg, sometimes gadfly and well known commentator on science policy, was on target when he noted that "Beginning about the second decade of this century, the folklore of scientific independence, admirable and inspiring as it might be, was rapidly eroded by raw economics. Nature no longer has much to reveal to the dilettante or the bare-handed investigator."<sup>2</sup>

Among the topics that we must take into account as we engage in strategic planning for medical research at the NIH, are such disparate matters as: new forms of collaboration with industry; biotechnology; the massive research effort against AIDS; the encounter with "big science" in the human genome project; the growing need for trained scientists; and such current issues as the use of animals in research and general concerns over misconduct in science, and the serious need for renovation and replacement of facilities.

## BIOTECHNOLOGY

As a result of significant gains in understanding the basic processes of life, biotechnology has emerged as a major new economic force in the world, and it offers great promise of benefit.

The prime examples of biotechnology stem from recombinant DNA. Investigators have been conducting research with this new technique since

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the 1970s. In the beginning, concerns were raised in the scientific community regarding the potential risks of applying this powerful new tool without adequate information to ensure the safety of the general population and those involved with the technology. The NIH took the lead in developing and continuously updating guidelines to cover research with recombinant DNA, but they were never intended to cover development and commercialization of genetically engineered organisms. Other Federal agencies have jurisdiction over these areas. To provide a forum for interagency coordination on such matters, the Biotechnology Science Coordinating Committee was chartered. It reports to the President's science advisor and consists of representatives from EPA, USDA, NSF, FDA, and NIH. I currently am chairman of the committee.

Internationally the Organization for Economic Cooperation and Development provides an informal forum for coordination of the application of regulations to biotechnology. Through it we hope to avoid major differences in the application of guidelines among participating nations; to share experiences and to avoid unnecessarily restraining development through an excess of caution leading us to tie our own hands.

The NIH has a serious commitment to maintaining the science base necessary to fuel further advances in biotechnology. NIH also will continue to participate in efforts to understand the effects of the applications of genetic engineering techniques to ensure their safe and productive use.

#### NEW PARTNERSHIPS

In the years since the modern NIH was established in the late 1940s, our research activities have been carried out in large part through a two-way partnership where the Federal Government joined with academic institutions, hospitals or nonprofit laboratories. The partnership has now been expanded to include industry.

Industry's share of the nation's investment in biomedical research has been making rapid gains in recent years. As recently as 1981 the total spent by all of American industry for health-related research and

development was less than the research budget of NIH alone. By 1987 this had changed, and industry was spending about \$6.8 billion annually for health research and development, compared with NIH's research expenditures of \$5.5 billion. New policies and interests are now bringing about a degree of convergence between industry and the government.

For example, the Federal Technology Act of 1986 provides incentives that are stimulating accelerated interest in formal collaboration between government laboratories and industry. The intent of Congress in passing the Technology Transfer Act was to assure that the results of government-conducted research became available to the public through patenting and commercial licensing of inventions, and further to improve America's competitive position in the world marketplace.

#### AIDS

The urgency and level of scientific, public, and political concern over the AIDS epidemic are manifest in one of the largest and most intensive research efforts ever mounted. There are a number of elements in the current situation that bring to mind the opening stages of the war on cancer in the early 1970s. Once again the NIH is committed to providing the leadership and direction necessary to marshal the resources and talents of the biomedical research community to combat a dreaded disease. The NIH is making every effort to ensure that AIDS research proceeds expeditiously. We have established an office of AIDS research within the Office of the Director that will act as a focal point for AIDS research. The purpose of the office is to coordinate the NIH AIDS research program, centralize various AIDS-related policy and operating functions, and represent the NIH Director on AIDS-related matters.

The Director of the National Institute of Allergy and Infectious Diseases, Dr. Anthony S. Fauci, now serves in a dual role as Associate Director for AIDS Research, and heads the new office. Dr. Fauci has been the NIH AIDS coordinator since 1985. At that time our AIDS research activities were concentrated largely in three institutes, but since then an almost tenfold expansion of AIDS efforts has occurred. The current annual budget is \$607 million, and essentially all components of NIH are now

involved. An AIDS Program Advisory Committee was chartered last year, and it is providing advice from the non-Federal research community and the public on overall AIDS-related research directions, scientific opportunities, policy questions, and major program initiatives to be undertaken by the NIH.

#### THE HUMAN GENOME PROJECT

The NIH has been the major player in the development of genetic information and in genetic research for the past several decades. In Fiscal Year 1987, NIH provided more than \$365 million for the study of the molecular biology of complex organisms, and most of our constituent institutes have been involved in such research. Although only a fraction of our expenditures has been used to support the mapping and sequencing of specific genes, the NIH has supplied much of the impetus for the development of new technologies for cloning and purifying DNA, making feasible the human genome project.

In FY 1988, NIH received \$17.3 million in new funding for a new research program to map and sequence complex genomes. The President's budget request for FY 1989 increased that amount to \$28 million.

In recognition of the high priority placed on mapping and sequencing the human genome and the over arching planning and resource demands of a systematic targeted effort, a new Office of Human Genome Research has been established within the Office of the Director, NIH, and will be headed by Nobelist James D. Watson as the Associate Director for Human Genome Research. The function of the office is to provide coordination, integration, review of progress, and planning in genomic analysis research. Research goals and long-range plans will be formulated with the guidance of a newly-chartered NIH Program Advisory Committee on the Human Genome and the NIH Working Group on the Human Genome. This strategy permits centralized coordination of the trans-NIH effort while maintaining the elements of peer review and program planning that are essential to a successful research initiative.

One of the key responsibilities of the new Office will be to coordinate the NIH planning process with the other Federal agencies and



research funding institutions involved. The NIH provides the lion's share of the Federal investment in genomic analysis. However, the Department of Energy and the National Science Foundation have a history of supporting research programs that are relevant to the genome project. There are already a number of joint projects under way that contribute to a national effort. At the working level, scientists funded by all three agencies collaborate on a number of investigations.

#### THE NEED FOR A CONTINUING SUPPLY OF TRAINED SCIENTISTS

To maintain the current pace of scientific advances, and particularly to press forward in carrying out initiatives such as biotechnology, the human genome project, and the great expansion of AIDS research, we must ensure that there is a continuing supply of bright and well-trained scientists. The Government-University-Industry Research Round Table of the National Academy of Sciences has been exploring issues relating to the identification, recruitment, development and retention of science and engineering talent. In evaluating the talent pool, the Round Table Group predicts that the demand for scientists and engineers will remain strong in both industry and academia, but that at the same time the numbers of Americans in the age groups that normally would be expected to be in training for those careers will be declining. For example, the current number of 22-year-olds is projected to drop by more than 25 percent before the end of this century. Even if the current number were not to decline, a significant increase in the proportion of 22-year-olds attaining scientific and engineering degrees would be required to meet the projected research needs. The Round Table Group estimated that to maintain the 1985 level of potential research trainees into the 1990's the degree award rate would have to increase by 30 percent. Unfortunately the number of baccalaureate degrees awarded in the life sciences has decreased steadily since 1977 to the present.

The number of full-time graduate students in the biological sciences has risen by about 1,000 during each of the past two years, after a six-year period of little or no change, but foreign students accounted for most of the increase. In 1987 there were about 38,000 such graduate students in the biological sciences and about one-fourth of them were foreign nationals.

There also have been steady increases in the number of postdoctorates and other faculty research staff in the biological sciences since 1980. The proportion of underrepresented minorities among graduate students who are U.S. citizens is 5.4 percent. The minority representation is low, but reflects a continuing improvement since 1981 when it was only 3.7 percent. However, the message is clear. If we are to realize the promises implicit in the recent and rapid gains in the biosciences, we must attract greater numbers from a diminishing age group of our population.

#### OTHER ISSUES

A substantial portion of the strategic planning for major programs of the NIH takes place on Capitol Hill. A current example is the creation of a new National Institute on Deafness and Other Communication Disorders (NIDCD). The Act authorizing NIDCD was signed by the President on October 29. The thirteenth NIH institute will be created by the transfer of a portion of the appropriation and programs of the National Institute of Neurological and Communicative Disorders and Stroke. The 1989 appropriation for the new institute comes to a total of \$96.1 million, and its structure and purposes will parallel those of the existing institutes of NIH.

Permit me now to mention briefly a few other issues that are of concern as we formulate our approach to the challenges of the years ahead. One such issue is the escalating controversy between the biomedical research community and animal welfare advocates concerning the use of animals in research. Federally supported laboratories have been the targets of illegal break-ins; theft of animals; and destruction of property, equipment and valuable records. The NIH has been the site of a sit-in, prolonged picketing, and two recent demonstrations by animal rights activists.

The introduction of legislation concerning various aspects of animal welfare is increasingly common in Congress and in State legislatures. About one-fourth of the states have enacted legislation prohibiting the release of pound animals for research use. In this connection I should point out that NIH neither specifies nor proscribes the sources of animals to be used in the biomedical research that it supports or conducts. It is

our position that animals selected for research projects must be of appropriate species, number and quality as determined by the investigator.

Eleven bills on different aspects of the care and use of animals in research were introduced in the 100th Congress. While we were in agreement with the intent of several of the bills, some of them could have severely hindered NIH-funded biomedical research efforts if enacted as proposed. We believe that by working closely on these matters with the Congress and with other government agencies, it will be possible for the NIH to serve both the public need for new measures for the improvement of health and the public's desire for the appropriate care and use of animals in biomedical research.

Recently, considerable public attention has been drawn to the issues surrounding what is known as misconduct in science. Although I personally believe that biomedical scientists equal or surpass any other professional group for integrity, and high purpose, one must admit that recent substantial examples of dishonesty have severely damaged public confidence in our enterprise. Misconduct and dishonest behavior in science, though infrequent, are so serious and undermining to the creation of a sound knowledge base in biomedical science that it is of great concern to all participants in research, as well as to the American public. It is our policy that grantee and contractor institutions receiving NIH research support have the primary responsibility for dealing with possible misconduct involving their scientists. This responsibility includes the duty to conduct inquiries or investigations as appropriate, and to inform and cooperate with NIH as the funding agency. It is not known whether the incidence of misconduct in science itself has risen within the past decade or so, but it is clear that reports of misconduct have increased in number, requiring NIH to make more explicit the procedures to deal with this phenomenon and to develop ways to prevent such behavior.

Since 1982 NIH has dealt with approximately 100 cases. In them, the alleged wrongdoing ranged from deliberately deceptive or fraudulent practices, such as fabrication and falsification of data, to honest errors in judgment or practice, or in some instances scientific disputes.



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Grantee institutions have been expanding their efforts during the past several years to monitor, investigate, and report research misconduct involving Federal funds, and to promote quality assurance and accountability in the conduct of science. However, there is still a far too prevalent reluctance on the part of universities and other grantee institutions to engage this unpalatable issue. Recent history shows that unless an institution has a well-planned mechanism in place, they will surely mess up when their first misconduct or fraud case occurs.

To provide for more efficient operation on our part, the NIH has increased core staff within the Office of Extramural Research to improve response time in handling cases under review, provide more extensive liaison with the research institutions conducting NIH-sponsored research, and facilitate ways to gather data and seek guidance from the extramural scientific community and from within the NIH scientific community.

On September 19, Notices of Proposed Rulemaking were published in the FEDERAL REGISTER by DHHS and NIH on the responsibilities of awardee and applicant institutions for dealing with possible misconduct in science and the development of protective regulations. Public comments were requested on issues raised by the proposed regulations such as the organizational location of the Office of Scientific Integrity and the need to be certain that strong scientific review is the first component of any inquiry. It is essential in dealing with these matters that our efforts to remedy current problems not lead to the development of a vigilante or "ethics cop" mentality with such actions as random unannounced site visits to research labs and data notebook reviews, such as are currently being advocated by some congressional committees.

One last item concerns our nationwide need for research facilities. New scientific discoveries and the development of new technologies are changing the nature of research needs and require more sophisticated facilities to accommodate the new research. There is also a substantial backlog of needed repair, renovation, and replacement of facilities and equipment. Decades-old laboratory buildings may be structurally sound, but the support systems and interior architectural features are increasingly



inadequate or deteriorated. There is also need to meet new requirements for hazardous chemical and biological materials, laboratory animal facilities, handicapped access requirements, and energy conservation requirements.

In 1987 the Congress asked NIH to convene a group of consultants to address the specifics of this serious problem.

The study group, representative of the key leadership of colleges, universities and nonprofit research institutions, met in February this year and not unexpectedly found that there is an urgent need for developing a well-coordinated, long-range national strategy for a research facilities construction program.

The group recommended a 10-year NIH Research Facilities Construction Program, including a 2-year pilot phase to help shape the longer term effort.

The report of the study group has been transmitted to the Congress. We recognize that the issues related to funding these research facilities are complex and embedded in the context of Federal fiscal constraints, and that no simple or easy solution is in sight.

There are many other important topics and issues bearing on the long-term health of the biomedical research enterprise that deserve--in fact, demand--our attention as members of the biomedical research community in the Federal Government, in academia, in health care, or in industry.

I have discussed a few key issues today, and time permitting, would be glad to respond to questions or comments.

#### REFERENCES

<sup>1</sup>Thomas, Lewis, "The Medusa and the Snail," Viking Press, New York, 1979, p 73.

<sup>2</sup>Greenberg, Daniel, "The Politics of Pure Science," New American Library, Inc., New York, 1967, p 62.

REMARKS\*

BY

JAMES B. WYNGAARDEN, M.D.\*\*

GOOD MORNING.

IT IS A PLEASURE FOR ME ON BEHALF OF THE NATIONAL INSTITUTES OF HEALTH AND THE PUBLIC HEALTH SERVICE TO HOST TODAY'S PROGRAM IN RECOGNITION AND IN SUPPORT OF WORLD AIDS DAY, WHICH WILL OFFICIALLY TAKE PLACE TOMORROW, ON DECEMBER 1ST.

JOINING ME TODAY ARE FOUR INDIVIDUALS WHO HAVE PLAYED PROMINENT ROLES IN OUR NATIONAL AND INTERNATIONAL EFFORTS AGAINST HIV. IT IS MY PRIVILEGE TODAY TO SHARE THE PODIUM WITH DR. ROBERT WINDOM, OUR ASSISTANT SECRETARY FOR HEALTH, DR. CARLYLE GUERRA DE MACEDO, DIRECTOR OF THE PAN AMERICAN HEALTH ORGANIZATION, ADMIRAL JAMES WATKINS WHO CHAIRED THE PRESIDENT'S COMMISSION ON THE HUMAN IMMUNODEFICIENCY VIRUS EPIDEMIC AND DR. ANTHONY FAUCI, ASSOCIATE DIRECTOR FOR AIDS RESEARCH AT NIH.

THE CONCEPT FOR AND SPONSORSHIP OF WORLD AIDS DAY EVOLVED THROUGH THE EFFORTS OF THE WORLD HEALTH ORGANIZATION GLOBAL PROGRAM ON AIDS.

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\*WORLD AIDS DAY, NOVEMBER 30, 1988, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND.

\*\*DIRECTOR, NATIONAL INSTITUTES OF HEALTH.

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THE NATIONAL INSTITUTES OF HEALTH, AS A WHO COLLABORATING CENTER ON AIDS AND AS THE LEADING SUPPORTER OF BIOMEDICAL RESEARCH IN AIDS HAS ESTABLISHED A SPECIAL RELATIONSHIP WITH THE WORLD HEALTH ORGANIZATION IN A COLLECTIVE EFFORT AGAINST THIS DREAD DISEASE.

AS OF THE END OF SEPTEMBER, OVER 140 COUNTRIES HAVE REPORTED NEARLY 120,000 CASES OF AIDS, A FIGURE THAT IS THOUGHT TO BE QUITE LOW DUE TO UNDERREPORTING. INDEED, THE NUMBER OF ACTUAL CASES MIGHT WELL EXCEED 200,000. IN THE UNITED STATES ALONE, THERE HAVE BEEN NEARLY 80,000 CASES OF AIDS REPORTED TO DATE.

THE THEME OF WORLD AIDS DAY IS TO "TELL THE WORLD WHAT YOU ARE DOING ABOUT AIDS." SINCE FISCAL YEAR 1982, THE NATIONAL INSTITUTES OF HEALTH HAS SPENT \$996 MILLION IN SUPPORT OF AIDS RESEARCH. DURING FISCAL YEAR 1989, THE NIH WILL SPEND \$588 MILLION ON AIDS RESEARCH AND RELATED ACTIVITIES. TO COORDINATE THIS IMPORTANT NIH-WIDE EFFORT, WE HAVE ESTABLISHED AN OFFICE OF AIDS RESEARCH WITHIN MY IMMEDIATE OFFICE HEADED BY DR. FAUCI.

A RECENT SURVEY OF INTERNATIONAL ACTIVITIES RELATED TO AIDS INDICATES THAT THE NATIONAL INSTITUTES OF HEALTH PLANS TO SPEND OVER \$20 MILLION ON SUCH ENDEAVORS DURING FISCAL YEAR 1989. MANY NIH PROGRAMS ARE IN DIRECT SUPPORT OF THE WHO GLOBAL PROGRAMME IN AIDS. A MAJOR GOAL OF THE WHO IS TO SUPPORT RELEVANT INTERNATIONAL RESEARCH AND TO STRENGTHEN AIDS PREVENTION AND OPERATIONAL RESEARCH IN DEVELOPING COUNTRIES OF THE WORLD THREATENED BY THE SPREAD OF HIV. I EXPECT WE WILL HEAR MORE ABOUT THIS FROM DR. MACEDO.

EXAMPLES OF NIH PROGRAMS IN SUPPORT OF THE GLOBAL EFFORT AGAINST HIV INCLUDE THE NIAID PROGRAM OF INTERNATIONAL COLLABORATION IN AIDS RESEARCH (ICAR) AND THE PROGRAMS OF THE FOGARTY INTERNATIONAL CENTER FOR INTERNATIONAL TRAINING GRANTS IN EPIDEMIOLOGY RELATED TO AIDS AND INTERNATIONAL POSTDOCTORAL RESEARCH AND TRAINING GRANTS IN AIDS.

AS WE DEVELOP OUR INTERNATIONAL AIDS RESEARCH PROGRAMS, HOWEVER, WE MUST CONTINUE TO BE SENSITIVE TO A NUMBER OF ISSUES. FIRST, RESEARCH IN COLLABORATION WITH DEVELOPING COUNTRIES SHOULD BENEFIT THE PEOPLE OF THOSE COUNTRIES AS WELL AS THE DEVELOPED WORLD. THE NEEDS AND PRIORITIES OF OTHER COUNTRIES MUST BE CONSIDERED IN THE DESIGN OF RESEARCH PROGRAMS. OUR INTERNATIONAL RESEARCH MUST MEET THE SAME HIGH SCIENTIFIC AND ETHICAL STANDARDS THAT WE DEMAND FOR OUR DOMESTIC RESEARCH. AT THE COMPLETION OF OUR RESEARCH WE SHOULD ALSO HAVE MADE PROGRESS IN STRENGTHENING THE RESEARCH INFRASTRUCTURE IN THE HOST COUNTRY SO THAT WE CAN FACILITATE THE CONDUCT OF FURTHER RESEARCH. FINALLY, WE MUST ACTIVELY SHARE THE RESULTS OF OUR RESEARCH WITH THE HOST COUNTRY.

THE NEED FOR INTERNATIONAL COOPERATION AND COLLABORATION HAS NEVER BEEN GREATER. ONLY THROUGH A WORLDWIDE EFFORT CAN WE HOPE TO WIN THE BATTLE AGAINST AIDS.

LET ME NOW INTRODUCE DR. ROBERT WINDOM, ASSISTANT SECRETARY FOR HEALTH. DR. WINDOM HAS LENT HIS CONSIDERABLE ENERGY AND ENTHUSIASM TO INCREASING NATIONAL AND INTERNATIONAL AWARENESS AND COOPERATION IN COMBATTING AIDS.





RESEARCH, TRAINING, AND THE CLINICAL INVESTIGATOR\*

by

James B. Wyngaarden, M.D.\*\*

In mid-November I participated in a Duke Medical Alumni scientific program honoring the emeritus chairman of the Department of Medicine, Eugene Stead. The several speakers addressed a variety of topics, including such future-oriented subjects as "An Academic Plan for Duke Medical Center" and "The Future Role of the University Medical Center in Quality Health Care." I spoke on "Strategic Planning for Research in the Medical Sciences."

That kind of examination of the future prospect of biomedical research encounters immediately the prominence of molecular biology at the frontiers of science and the remarkably accelerated pace of progress in other disciplines. Concurrent with these new and evolving changes in the scope of science are significant developments in the sociology and governance of the scientific enterprise. Some of the latter developments are as vital to future progress in science as are new understandings of nature.

Among such influences are: the launching of the human genome project; the emergence of biotechnology; the development of additional collaborative ties among industry, academia and the Federal Government; the massive research and education effort against AIDS; increasing pressures from animal activist groups; the need for renovation and replacement of research facilities countrywide; public concerns about possible misconduct in science; and the predicted shortage of trained scientists.

Of this roster of current concerns, the one I mentioned last--the need for trained scientists--is probably the most significant.

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\*Presented at New York Hospital, Cornell Medical Center,  
New York City, December 4, 1988.

\*\*Director, National Institutes of Health, Bethesda, Maryland

## THE NEED FOR A CONTINUING SUPPLY OF TRAINED SCIENTISTS

To maintain the current pace of scientific advances, and particularly to press forward in carrying out initiatives such as biotechnology, the human genome project, and the great expansion of AIDS research, we must ensure that there is a continuing supply of bright and well-trained scientists. From the perspective of 1988 the outlook is sobering.

The Government-University-Industry Research Round Table of the National Academy of Sciences has been exploring the broad outlines of this need, particularly issues relating to the identification, recruitment, development and retention of science and engineering talent. In evaluating the talent pool, the Round Table Group predicts that the demand for scientists and engineers will remain strong in both industry and academia, but that at the same time the numbers of Americans in the age groups that normally would be expected to be in training for those careers will be declining. For example, the current number of 22-year-olds is projected to drop by more than 25 percent before the end of this century. Even if the current number were not to decline, a significant increase in the proportion of 22-year-olds who elect to pursue scientific and engineering degrees would be required to meet the projected research needs. The Round Table Group estimated that to maintain the 1985 level of potential research trainees into the 1990's the degree award rate would have to increase by 30 percent. Unfortunately, the number of baccalaureate degrees awarded in the life sciences has decreased steadily since 1977 to the present.

It is true that after a six-year period of little or no change the number of full-time graduate students in the biological sciences has risen by about 1,000 during each of the past two years, but foreign students accounted for almost all of the increase. In 1987 there were about 38,000 such graduate students in the biological sciences, and about one-fourth of them were foreign nationals. The message is clear. If we are to realize the promises implicit in the recent and rapid progress in the biosciences, we must attract greater numbers from a diminishing age group of our population.

The seriousness of our predicament was underlined recently in a comment by Dale Corson, president emeritus of Cornell University. In an article on the nation's technological future that appeared in the WASHINGTON POST last Monday, Dr. Corson stated his opinion that "Children are being turned off to science beginning the first day of first grade." He warned that "The problem is so deep that I think it will take generations to solve."<sup>1</sup> While we can hope that things turn out differently, such a forecast gives notice that the challenge we face is daunting indeed, particularly when we consider the current and future needs for such categories as investigators trained for clinical research.

Since the inception of NIH, the interdependence of training and research has been recognized. This linkage provides the opportunity for the development of the next generation of scientists in the same laboratories where new discoveries are being made. The NRSA and Research Career Programs of NIH serve several functions: they attract students to research careers; they enhance research environments; and most of all they represent what has been an effective effort to ensure the Nation's research enterprise by maintaining the flow of well-trained young scientists into research careers.

Since 1971, training funds administered through NIH after adjustment for inflation have declined by almost 6 percent per year, while at the same time expenditures for research have increased by 3 percent per year. Nevertheless, NIH has been able to maintain a relatively stable number of trainees by such measures as restricting stipends to levels that have become unrealistic. After four years without an increase it has become essential that we adjust the stipend level, but doing so in the absence of a concomitant increase in funding for training forces a reduction in the number of trainees that can be supported.

Applications for training grants supported through the NIH institutes are customarily reviewed during the January round of National Advisory Council meetings. It appears that at the upcoming Council reviews, most of the institutes will limit sharply the number of awards for institutional training grants. For example, notices have been sent to applicants, whose



proposals are to be reviewed by the National Advisory Neurological and Communicative Disorders and Stroke Council, that there is a real possibility that no new or competing awards can be made. Recognizing that competitive renewal applicants have trainees currently being supported on their training grants, efforts will be made to provide limited support for trainees who were appointed before September 1 of this year and are eligible for reappointment. Additional information will be provided as the year progresses.

As a footnote, I should explain that since the National Advisory Council for the new Deafness Institute has not been established, the NINCDS Council will act on training grants that will be funded through NIDCD. The figures I have cited are aggregated and relate to both institutes.

Let me return now to the general subject of training. All involved agree that research training of clinicians is an especially critical matter. The need for clinical research training is evident, but such training exacts a substantial financial sacrifice of the physician trainee, particularly those who have invested in or face costly years of advanced specialty training. There is no way that a stipend can offset the income that a highly trained specialist must forego for research training. The dilemma is experienced by institutions as well as individuals, for the changing financial structure in research-intensive medical institutions places more emphasis on patient-care revenues to the detriment of clinical research.

Within biomedical research activities a new sub-enterprise--clinical trials--has developed and is undergoing rapid growth in terms of the numbers of participating investigators and subjects. Such studies as the "TIMI" (Thrombolysis in Myocardial Infarction) trial, the "Tight Control Diabetes Trial" (Diabetes Control and Complications Trial), and the just-beginning (Dec. 12) Modification of Diet in End Stage Renal Disease Trial not only require large numbers of investigators, but their results are of major potential significance with respect to the long-term efficacy of medical care as well as its cost.

Members of the Congress who have interest and responsibility in the general area of health care and biomedical research show an increasing level of interest in the number of clinical trials now being supported through the NIH, and consequently in the training of investigators for the conduct of such trials. In our recent budget and other hearings on the Hill we have come to expect questions about clinical trials and other evidence of interest on the part of the Members in assisting us to strengthen this kind of research.

The rapid expansion of this important activity suggests that we might well reexamine some of the premises on which we have developed and conducted our programs of research training. I am making no proposal, nor attempting to describe what might be done, but rather I am raising a question for your consideration. Our research training programs have not been oriented specifically toward filling the emerging need for persons competent to carry out clinical trials where shortages will become acute. Should we structure our training programs in a different way, particularly those that we expect to prepare clinical investigators?

Thinking about this question has brought to mind the impression that of late there has been a gradual change in the career course of physician-investigators. A fairly typical path followed by my physician contemporaries, who had deep interest in biomedical research, was to enter an intensive program of postdoctoral research training and experience after completing medical school and their specialty residency. During such training experience most of us had the intention of returning to clinical care either within an academic institution or in full-time practice. From this population sponsors of clinical trials have drawn the best-qualified investigators available for conducting the trials, scientists who were active in the clinical care setting and in a position to participate in such activities. A drawback with this pattern under current circumstances is the advanced level of expertise required for the planning and conduct of the more complex trials. Even though my contemporaries and I had solid postdoctoral research training it did not confer upon us all-purpose qualifications. There may now be a new and even more serious drawback.

There appears to be a trend for the persons who have followed the career path I have described to finally opt out of clinical care.

Perhaps we should look to well-trained clinical specialists and provide them with the advanced training in such areas as epidemiology and biostatistics with the thought that such training would prepare them for the sound planning and conduct of clinical trials in the areas of their expertise. Could such trained specialists be induced to take one or two years of training specific to the requirements for clinical trials?

Having suggested that it might be useful to rethink our training programs as they contribute to our ability to conduct clinical trials, permit me to turn now to another aspect of the matter about which my conclusions are much more definite. I refer to another effect of biomedical research, including in particular clinical trials---the creation of a new set of ethical issues. The problems arise in large part because of the financial consequences--some of them massive--that are bound up with the results of clinical trials. The appearance of conflict of interest is a potential trap for every investigator involved in conducting a clinical trial. For responsible investigators to have consultancy arrangements with industrial parties-at-interest, or to own stock in such companies, or to accept stock options in them is to invite personal embarrassment at least. While under most circumstances trials have been planned with such care that the results are not likely to be tainted with the questionable ethics of a few participants, the effect on the public's perception of scientists and science in general can be devastating. I think we must give much more attention to the appearance and certainly to the reality of conflicts of interest as they pertain to investigators involved in clinical trials.

#### THE HUMAN GENOME PROJECT

The NIH has been the major player in the development of basic genetic information and in the support as well as the conduct of genetic research for the past several decades. It has supplied much of the impetus for the development of new technologies for the cloning and purifying of DNA, making feasible the human genome project.

In FY 1988 the Congress added \$17.3 million in new funding to the NIH appropriation for a new research program to map and sequence complex genomes. In the President's request for the current year's budget, subsequently approved by the Congress, the budget for the genome project was increased to \$28 million. Thus, we were assured that both the Congress and the White House were supportive of the initiative, were willing to provide special funding for it, and that we could embark upon this major program without threatening ongoing and necessary research activity in other areas.

Consequently we have established a new Office of Human Genome Research within the office of the NIH Director. It is headed by Nobelist James D. Watson as the Associate Director for Human Genome Research. The office is to provide coordination, integration, progress review and planning in genomic analysis research. Dr. Watson will formulate research goals and long-range plans with the advice and assistance of his staff and a newly chartered NIH Program Advisory Committee on the Human Genome. Together the components of the genome office will provide centralized coordination of the trans-NIH effort while maintaining the elements of peer review and program planning that are essential to a successful research initiative. The NIH provides a lion's share of the Federal investment in genomic analysis, but the Department of Energy and the National Science Foundation have a history of supporting research programs that are relevant to the genome project. A number of joint projects are already underway, and at the working level, scientists funded by all three agencies are collaborating on a number of investigations.

#### BIOTECHNOLOGY

As a result of significant gains in understanding the basic processes of life, biotechnology has emerged as a major new economic and beneficial force in the world. The best known applications of biotechnology stem from recombinant DNA.

Investigators have been conducting research with recombinant DNA since the early 1970s. The history of this innovation provides an example of how



social concerns can exert a marked influence on the progress of science. At the outset, questions were raised by the scientists responsible for developing the technique regarding the possible risks of applying this new tool without adequate information to ensure the safety of the general population and those involved with the technology. The NIH took the lead by developing and maintaining guidelines to cover research with recombinant DNA. We made no attempt, however, to cover development and commercialization of genetically engineered organisms. Other Federal agencies have jurisdiction over these areas.

An informal international forum for coordination of the application of regulations to biotechnology has been established. Through it we hope to avoid major differences among participating nations, and particularly to avoid unnecessary restraints on development through an excess of caution.

#### NEW PARTNERSHIPS

For the past 40 years NIH research activities have been carried out in large part through a two-way partnership between the Federal Government and private non-profit entities, such as academic institutions, hospitals and free-standing laboratories. In recent years, a third category of partners has joined the national biomedical research endeavor, so that now industry, academia, and the government work closely in mutually supportive efforts.

New and productive modes of collaboration between industry and academic organizations have developed in the current decade involving such well-known organizations as Hoechst with Massachusetts General Hospital, Exxon with Massachusetts Institute of Technology, and Monsanto with Washington University. A new organizational approach was announced last week by The Johns Hopkins University and The Johns Hopkins Health System. They will join with corporate investors to form a new for-profit corporation whose purpose will be to transfer technology from the university laboratories to the marketplace. Although not a party to the arrangement, the Federal Government has substantial interest. The John Hopkins University received more Federal research funds last year than any other university in the nation.

Industry's share of the nation's investment in biomedical research has been making rapid gains in recent years. As recently as 1981 the total spent by all of American industry for health-related research and development was less than the research budget of the NIH alone. By 1987 this had changed and industry was spending \$6.8 billion annually for health research and development compared with NIH's research expenditures of \$5.5 billion. As would be expected, the bulk of industry's expenditures were concentrated at the development end of the spectrum and NIH's outlays were for research--most of it for basic investigations. New policies and interests, however, are now bringing about a degree of convergence between industry and the government.

#### AIDS

The urgency and level of scientific, public, and political concern over the AIDS epidemic are manifest in one of the largest and most intensive research efforts ever mounted. There are a number of elements in the current situation that bring to mind the opening stages of the "War on Cancer" in the early 1970s. Once again NIH is committed to providing the leadership and direction needed for marshaling the resources and talents of the biomedical research community to combat a dreaded disease. The NIH is making every effort to ensure that AIDS research proceeds expeditiously. We have established an Office of AIDS Research within the office of the NIH Director that will act as a focal point for AIDS research. The purpose of the office is to coordinate the NIH AIDS research program, centralize various AIDS-related policy and operating functions, and represent the NIH Director on AIDS-related matters.

The Director of the National Institute of Allergy and Infectious Diseases, Dr. Anthony S. Fauci, now serves in a dual role as NIH Associate Director for AIDS Research and heads the new office. Dr. Fauci has been the NIH AIDS coordinator since 1985 when our AIDS research activities were concentrated largely in three institutes. Since that time an almost tenfold expansion of AIDS efforts has occurred so that the current annual budget is \$607 million, and essentially all components of NIH are now involved.

## OTHER ISSUES

I will mention a few other developments, some of which may be of special interest to investigators in the neurosciences and related fields.

One such development is the creation of a new National Institute on Deafness and Other Communication Disorders (NIDCD). The Act authorizing NIDCD was signed by President Reagan on October 29. The thirteenth NIH institute will be created by the transfer of a portion of the appropriation and programs of the National Institute of Neurological and Communicative Disorders and Stroke. The appropriation for NIDCD for FY 1989 was set at \$96.1 million, and the structure of the new organization will be similar to that of the existing institutes.

All of the medical disciplines, and particularly the neurosciences, have a major stake in the escalating controversy between the biomedical research community and animal welfare advocates concerning the use of animals in research. Federally supported laboratories have been the targets of illegal break-ins; theft of animals; and destruction of property, equipment and valuable records. The NIH has been the site of a sit-in, prolonged picketing, and two recent demonstrations by animal rights advocates.

The introduction of legislation concerning various aspects of animal welfare is increasingly common in Congress and in State legislatures. About one-fourth of the states prohibit by law the release of pound animals for research use. In this connection I should point out that NIH neither specifies nor proscribes the sources of animals to be used in the biomedical research that it conducts or supports. It is our position that animals selected for research projects must be of appropriate species, number, and quality as determined by the investigator.

Recently, considerable public attention has been drawn to the issues surrounding what is known as misconduct in science, including the conflict of interest problems I mentioned in connection with clinical trials. Although I personally believe that biomedical scientists equal or surpass

any other professional group for integrity, and high purpose, one must admit that recent substantial examples of dishonesty have severely damaged public confidence in our enterprise. Misconduct and dishonest behavior in science, though infrequent, are so serious and undermining to the creation of a sound knowledge base in biomedical science that it is of great concern to all participants in research, as well as to the American public. It is our policy that grantee and contractor institutions receiving NIH research support have the primary responsibility for dealing with possible misconduct involving their scientists. This responsibility includes the duty to conduct inquiries or investigations as appropriate, and to inform and cooperate with NIH as the funding agency.

Since 1982 NIH has dealt with approximately 100 cases. In them, the alleged wrongdoing ranged from deliberately deceptive or fraudulent practices, such as fabrication and falsification of data, to honest errors in judgment or practice, or in some instances scientific disputes.

Grantee institutions have been expanding their efforts during the past several years to monitor, investigate, and report research misconduct involving Federal funds, and to promote quality assurance and accountability in the conduct of science. However, there is still a far too prevalent reluctance on the part of universities and other grantee institutions to engage this unpalatable issue. Recent history shows that unless an institution has a well-planned mechanism in place, it will not be able to deal promptly and adequately with the sudden onslaught of issues that arise when their first misconduct or fraud case occurs.

To provide for more efficient operation on our part, the NIH has increased core staff within the Office of Extramural Research to improve response time in handling cases under review, provide more extensive liaison with the research institutions conducting NIH-sponsored research, and facilitate ways to gather data and seek guidance from the extramural scientific community and from within the NIH scientific community.

On September 19, Notices of Proposed Rulemaking were published in the FEDERAL REGISTER by DHHS and NIH on the responsibilities of awardee and



applicant institutions for dealing with possible misconduct in science and the development of protective regulations. Public comments were requested on issues raised by the proposed regulations, such as the organizational location of the Office of Scientific Integrity and the need to be certain that strong scientific review is the first component of any inquiry. It is essential in dealing with these matters that our efforts to remedy current problems not lead to the development of a vigilante or "ethics cop" mentality with such actions as random unannounced site visits to research labs and data notebook reviews, such as are currently being advocated by some congressional committees.

One last item concerns the nationwide need for research facilities. New scientific discoveries and the development of new technologies are changing the nature of research needs and require more sophisticated facilities to accommodate the new research. There is also a substantial backlog of needed repair, renovation, and replacement of facilities and equipment. Decades-old laboratory buildings may be structurally sound, but the support systems and interior architectural features are increasingly inadequate or deteriorated. There is also need to meet new requirements for hazardous chemical and biological materials, laboratory animal facilities, handicapped access requirements, and energy conservation requirements. These matters have been brought to the attention of Congress, most recently in a report from a study group representative of the key leadership of colleges, universities and nonprofit research institutions. The group pointed to an urgent need for developing a well-coordinated, long-range, national strategy for a research facilities construction program and recommended a 10-year NIH Research Facilities Construction Program, including a 2-year pilot phase to help shape the longer term effort.

We recognize that the issues related to funding these research facilities are complex and embedded in the context of Federal fiscal constraints, and that no simple or easy solution is in sight.

There are many other important topics and issues bearing on the long-term health of the biomedical research enterprise that deserve--in

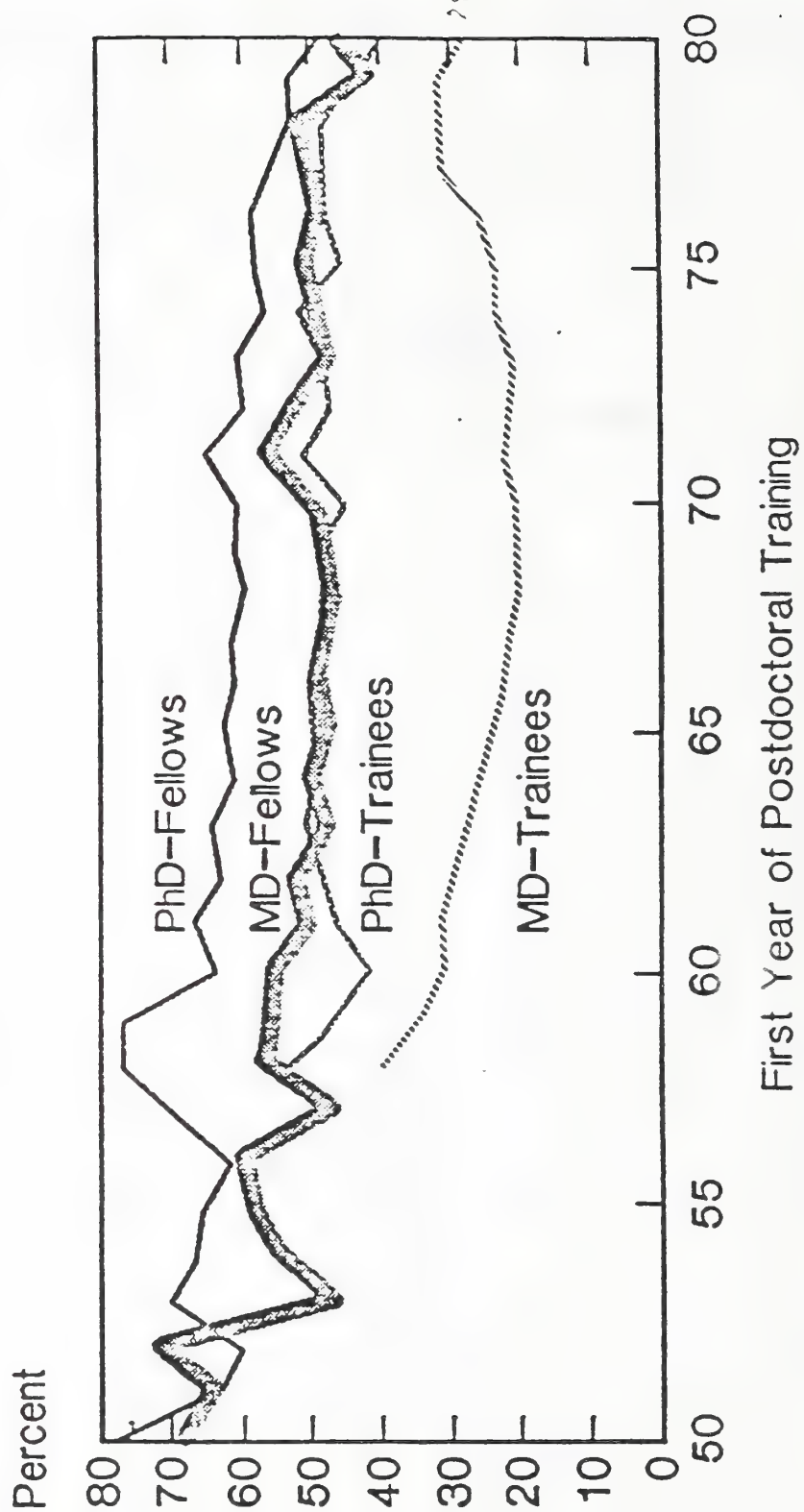
fact, demand--our attention as members of the biomedical research community in the Federal Government, in academia, in health care, or in industry.

I have discussed a few key issues today, and time permitting, would be glad to respond to questions or comments.

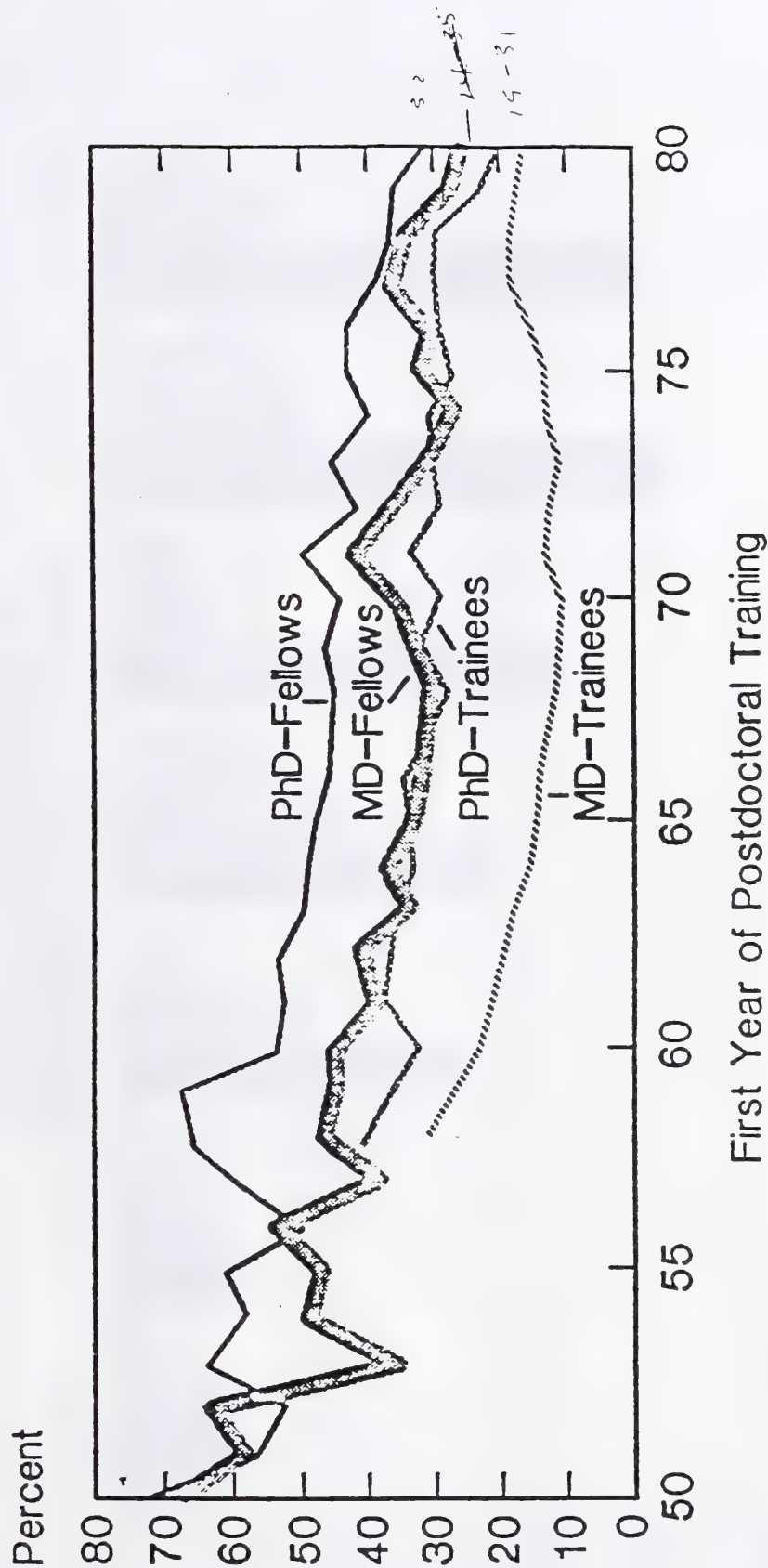
#### REFERENCES

- <sup>1</sup>Hilts, Philip J., WASHINGTON POST, Washington, D.C.,  
November 28, 1988, p. A15

# Percentage of NIH-Supported Postdoctorals Becoming NIH Grant Applicants, Fellows and Trainees, MDs and PhDs



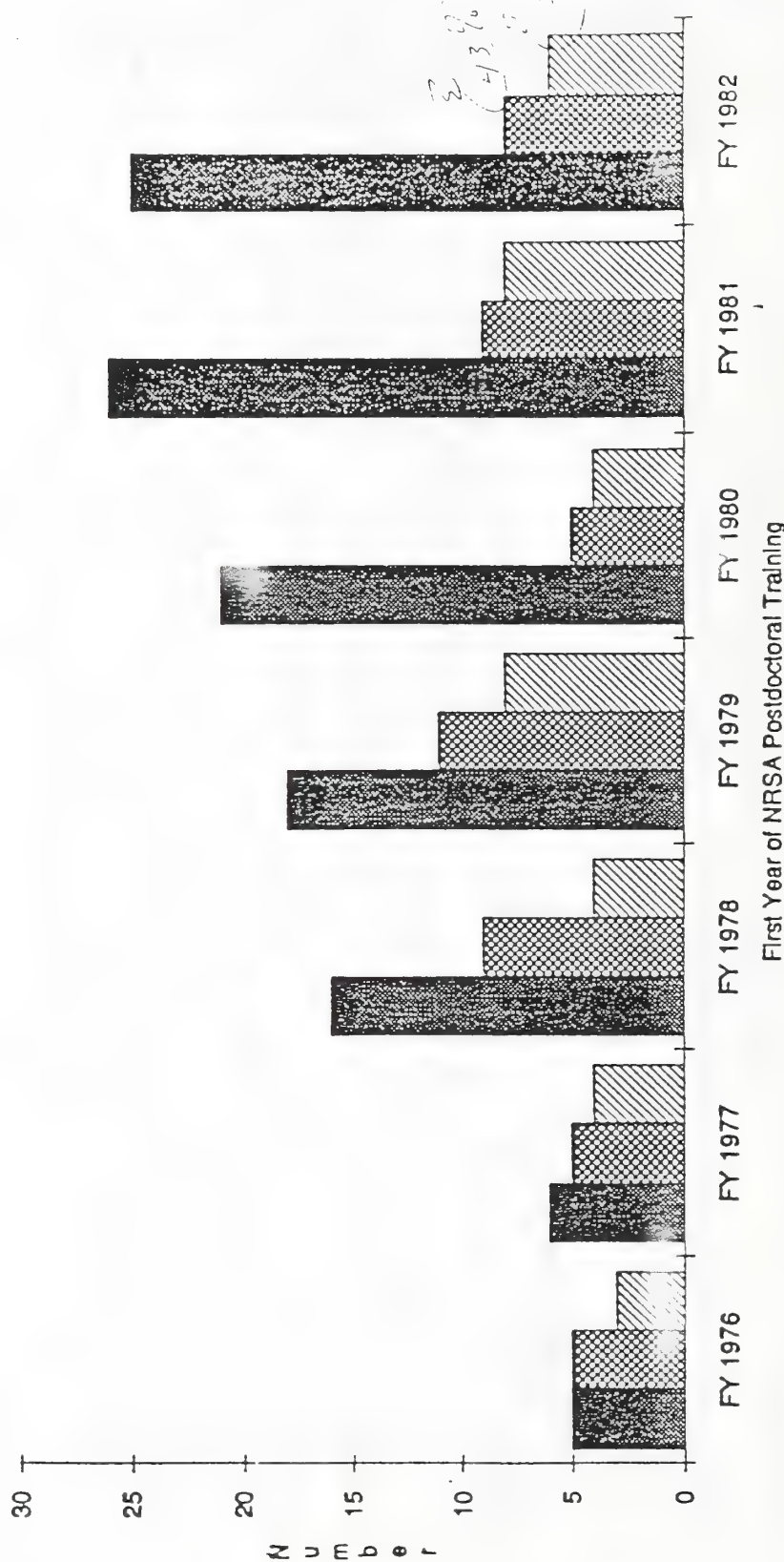
# Percentage of NIH-Supported Postdoctorals Becoming NIH Grant Recipients, Fellows and Trainees, MDs and PhDs



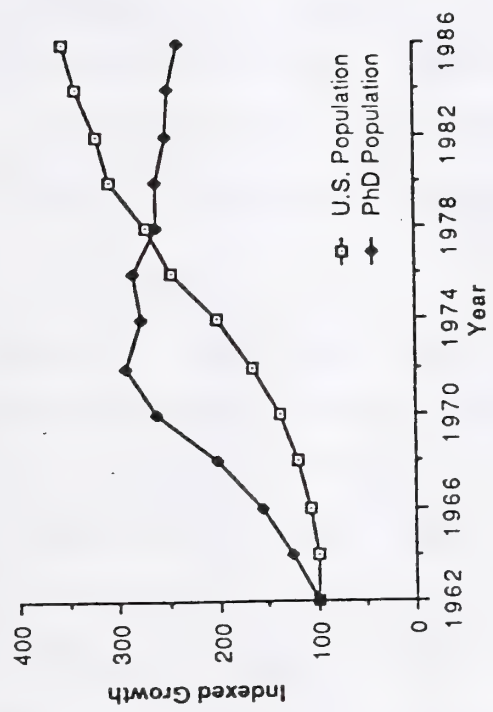


# NINCDS NRSA POSTDOCTORAL MD TRAINEES WHO BECAME NIH GRANT APPLICANTS AND AWARDEES (Trainees With Any Training)

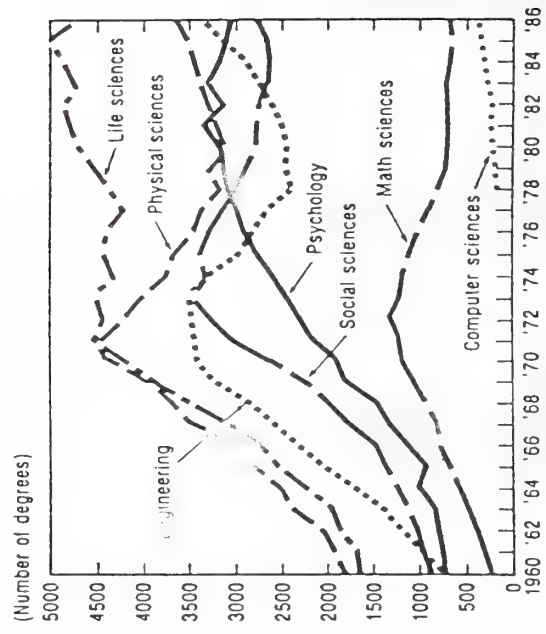
 Trainees
  Applicants
  Awardees



TRENDS IN THE NUMBER OF U.S. AND  
PERMANENT-RESIDENT Ph.D.s AND IN THE  
COMPARABLE U.S. POPULATION, 1962-1986



Science and engineering doctorates



TALKING POINTS FOR  
EPA BIOTECHNOLOGY SCIENCE ADVISORY BOARD MEETING  
DECEMBER 21, 1988

SUBCOMMITTEE CHAIRMAN: JAMES TIEDJE

O THANK YOU FOR PROVIDING THE OPPORTUNITY TO PRESENT COMMENTS ON BEHALF OF THE BIOTECHNOLOGY SCIENCE COORDINATING COMMITTEE ON THEIR SCIENTIFIC REVIEW OF THE EPA DRAFT PROPOSED BIOTECHNOLOGY RULES UNDER TSCA (TOXIC SUBSTANCES CONTROL ACT).

O AS BACKGROUND TO MY COMMENTS,

- BSCC WAS CHARTERED IN 1985 UNDER AUTHORITY OF THE FEDERAL COORDINATING COUNCIL FOR SCIENCE, ENGINEERING, AND TECHNOLOGY (FCCSET) (TAB 1) BY THE DIRECTOR, OFFICE OF SCIENCE AND TECHNOLOGY POLICY, EXECUTIVE OFFICE OF THE PRESIDENT.

WITH RESPECT TO BIOTECHNOLOGY, THE BSCC IS TO

- PROVIDE FOR INTERAGENCY SCIENCE POLICY COORDINATION AND GUIDANCE, AND
- PROMOTE "CONSISTENCY IN THE DEVELOPMENT OF FEDERAL AGENCIES' REVIEW PROCEDURES AND ASSESSMENTS."

O BASED ON THOSE FUNCTIONS AND ON EXECUTIVE ORDERS, SUCH AS E.O. 12291 (TAB 2), WHICH REQUIRE APPROPRIATE INTERACTIONS AMONG THE EXECUTIVE OFFICES OF THE PRESIDENT, THE BSCC WAS ASKED TO REVIEW THE SCIENTIFIC BASIS OF THE DRAFT PROPOSED TSCA RULES BY EPA AND, SUBSEQUENTLY, THE REVISED DRAFT RULES.



- THE CURRENT FORMULATION OF THE DRAFT RULES ARE ALSO CONTRARY TO THE INTENT OF EXECUTIVE ORDER 12591, FACILITATING ACCESS TO SCIENCE AND TECHNOLOGY (TAB 4). THIS EXECUTIVE ORDER, DATED APRIL 10, 1987, FOCUSED ON THE MEANS OF ENSURING THAT FEDERAL AGENCIES AND LABORATORIES ASSIST UNIVERSITIES AND THE PRIVATE SECTOR IN BROADENING OUR TECHNOLOGY BASE BY MOVING NEW KNOWLEDGE FROM THE RESEARCH LABORATORY INTO DEVELOPMENT OF NEW PRODUCTS AND PROCESSES.

- THE "INTENT" BASIS OF THE RULES REMAINS A MAJOR NEGATIVE FEATURE AND WILL HAVE A DAMPENING EFFECT ON COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENTS, RESULTING IN DECREASED COMPETITIVENESS OF THE U.S. BIOTECHNOLOGY INDUSTRY.

O THE BSCC HAS RECOGNIZED THE NEED FOR CLASSIFICATION SCHEMES BASED ON LEVEL OF RISK FOR MICROORGANISMS AND PLANTS, AND HAS TAKEN STEPS TO DEFINE RISK CATEGORIES.

BSCC MEMBERS HAVE PROVIDED FUNDING TO THE NAS FOR A STUDY (TAB 5) THAT WILL INCLUDE GUIDANCE TO BE USED IN ASSESSING POTENTIAL RISKS ASSOCIATED WITH INTRODUCTIONS INTO THE ENVIRONMENT OF MICROORGANISMS AND PLANTS.

- INITIAL PRIORITY IS BEING GIVEN TO DEFINING THOSE CATEGORIES OF LOWEST RISK.

- THE NAS STUDY SHOULD BE IN DRAFT FORM EARLY NEXT YEAR AND WOULD BE EXTREMELY HELPFUL TO REGULATORY AGENCIES IN STRUCTURING RISK-BASED RULES FOR BIOTECHNOLOGY, USING INPUT FROM AN INDEPENDENT AND HIGHLY EXPERT GROUP.

O THE PROPOSED RULES APPEAR TO IGNORE THE SUBSTANTIAL ADVANCES MADE IN BIOTECHNOLOGY SINCE THE COORDINATED FRAMEWORK WAS PUBLISHED IN 1986 AND HAVE THE POTENTIAL TO UNNECESSARILY RAISE REGULATORY BARRIERS TO BOTH BASIC RESEARCH AND THE COMMERCIALIZATION OF BIOTECHNOLOGY TO THE DISADVANTAGE OF THE COUNTRY. BY HINDERING INNOVATIVE DEVELOPMENTS IN A VARIETY OF ENVIRONMENTAL APPLICATIONS OF BIOTECHNOLOGY, SUCH AS TOXIC WASTE DISPOSAL, HEAVY METAL RECOVERY, POLLUTION CONTROL, AND SUBSTITUTES FOR CHEMICAL SUBSTANCES CURRENTLY USED FOR PLANT PROTECTION AND FERTILIZATION, OVER-REGULATION MAY BE COUNTERPRODUCTIVE TO THE OBJECTIVE OF PROTECTING HUMAN HEALTH AND THE ENVIRONMENT.

O THANK YOU. I WOULD BE WILLING TO ANSWER A FEW QUESTIONS NOW, BUT I WILL HAVE TO LEAVE VERY SHORTLY.

NOTES:

O DID NOT INCLUDE EBC'S, AS THAT VERGES ON REGULATION AND NOT SCIENCE. A PARAGRAPH ON EBC'S IS AT TAB 6.

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O THE BSCC REVIEW OF EPA'S PROPOSED RULES WAS TIME CONSUMING FOR ALL CONCERNED. THE BSCC WAS RESPONSIVE TO EPA'S CONCERNS AND POSTPONED COMPLETION OF ITS REVIEW THREE TIMES IN ORDER TO ALLOW FURTHER OPPORTUNITIES TO RESOLVE OUTSTANDING ISSUES.

O MEMBERS INDIVIDUALLY CONVEYED TO EPA A LARGE NUMBER OF SPECIFIC CONCERNS AND HELD EXTENSIVE DISCUSSIONS.

O BUT FUNDAMENTAL SCIENTIFIC CONCERNS REGARDING THE PROPOSED RULES REMAIN.

O THE MAJOR CONCERNS INVOLVE THE LACK OF SCIENTIFICALLY DETERMINED LIKELIHOOD OF RISK, AS EXEMPLIFIED BY

- PROCESS-BASED DEFINITIONS OF ORGANISMS TO BE REGULATED, AND
- "COMMERCIAL INTENT" OF THE R&D TO TRIGGER REGULATION.

O WITHOUT A RISK BASIS, AS OUTLINED IN THE COORDINATED FRAMEWORK OF JUNE 26, 1986 (TAB 3), THE PROPOSED RULES PORTRAY A GREATER DEGREE OF INHERENT RISK IN THESE MICROBIAL PRODUCTS THAN SCIENTIFIC EVIDENCE SUPPORTS.

- THE PROPOSED RULES WOULD REGULATE INTERGENERIC ORGANISMS AS DEFINED BY THE PROCESS OF THEIR FORMATION (THAT IS, BY DELIBERATE COMBINATION). THE RULES WOULD NEITHER REGULATE ACCORDING TO THE PRODUCT FORMED NOR THE CHARACTERISTICS OF THE PARENTS/DONORS.

- THE DISTINCTION BETWEEN "ALTERED MICROORGANISM" AND "NATURALLY OCCURRING MICROORGANISMS" IS NOT SCIENTIFICALLY BASED AND IS CONTRARY TO THE NIH APPROACH THAT ORGANISMS THAT RESULT FROM MANIPULATIONS THAT CAN BE CONSIDERED "SELF-CLONING" ARE EQUIVALENT TO WILD TYPE ORGANISMS. IN ADDITION, THE INTRODUCTION OF THE "ALTERED" CATEGORY WOULD NEGATE THE EXEMPTION OF "WELL CHARACTERIZED, NON-CODING REGULATORY SEQUENCES" FROM THE DEFINITION OF "INTERGENERIC", BECAUSE ORGANISMS MEETING CRITERIA FOR THE EXEMPTION WOULD STILL BE "ALTERED", AND, THEREFORE, REGULATED.

O USE OF "COMMERCIAL INTENT" FOR REGULATION OF R&D

- IS NOT SCIENCE OR RISK BASED.  
- THE SAME RESEARCH COULD BE REGULATED DIFFERENTLY ACCORDING TO THE INTERPRETATION OF COMMERCIAL INTENT.

- ATTEMPTS TO DEFINE COMMERCIAL R&D ILLUSTRATE THE COMPLEX RELATIONSHIPS BETWEEN UNIVERSITIES AND THE PRIVATE SECTOR AND RAISE SERIOUS CONCERNS REGARDING THE FUTURE OF INNOVATIVE BASIC RESEARCH. THE FORMS OF THESE RELATIONSHIPS AND NUMBERS OF AGREEMENTS ARE INCREASING RAPIDLY, ENCOURAGED BY THE FEDERAL GOVERNMENT AS A MEANS OF INCREASING THE COMPETITIVE POSITION OF THE U.S. IN THE WORLD MARKET.

- THE "INTENT" BASIS OF REGULATION IS COUNTER TO THE FEDERAL TECHNOLOGY TRANSFER ACT OF 1986 WHICH ENCOURAGES COMMERCIAL DEVELOPMENT OF IDEAS GENERATED IN THE COURSE OF FUNDAMENTAL RESEARCH.





## OPENING REMARKS AND CHARGE TO THE COMMITTEE\*

by

James B. Wyngaarden, M.D.\*\*

The National Institutes of Health has long been committed to the support of research on the genetics underlying human development and disease. Substantial amounts have also been provided for the characterization of the genomes of a variety of organisms and most of our constituent Institutes have been involved in such research. Some of our research has focused specifically on the molecular biology of human genetic diseases and in the course of this work we have supported the mapping and sequencing of specific genes.

Further, through its programs in molecular biology the NIH has supplied much of the impetus for the development of new technologies for cloning and purifying DNA, making possible the mapping and sequencing of the large genomes, including the human genome.

Thus we have the tools for at least initiating a targeted effort whose results can be expected to have a profound and beneficial impact upon our understanding of biological processes and ultimately upon our ability to prevent or treat human diseases of known genetic origin, and to understand other disorders having genetic components. Significantly, dedicated funding for the genome initiative is now being provided through the annual appropriations to the NIH. The first such earmarking for this purpose took place last year when the appropriation for Fiscal Year 1988 included \$17.2 million for the genome program. The amount was increased to \$27.6 million for the current fiscal year. In addition, appropriations were made last year in the amount of \$3.8 million and this year of \$7.9 million to the National Library of Medicine for a Biotechnology Information Center that will provide leadership in the development of the information handling capability essential to the human genome project.

From the outset we have seen that as research supporting an orderly exploration of the human and other genomes expands and accelerates, other agencies, private organizations, and individual scientists will be involved in the effort in this

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\*Presented at the First Meeting of the Program Advisory Committee on the Human Genome on January 3, 1989.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

country and abroad. The NIH provides a lion's share of the federal investment in genomic analysis through its regular programs plus the earmarked funds, but the Department of Energy and the National Science Foundation have a history of supporting programs that are relevant to the genome project. A number of joint projects are underway, and at the working level, scientists funded by all three agencies are collaborating on a number of investigations. It became increasingly clear, however, that for the NIH to continue to exercise leadership in this endeavor we must establish an organizational center to direct the project and to coordinate it with other federal and non-federal agencies, with industry, and with various national and international scientific organizations.

Accordingly, the NIH Office of Human Genome Research was created within the central administration of NIH. Official announcement of the establishment of the office was made September 26 last year and at that time I was delighted to make a public statement about a giant step forward for the program--the news that James D. Watson had accepted my invitation to head our effort as the NIH Associate Director for Human Genome Research. Dr. Watson brings to the position the experience of his unmatched career as a scientist and scientist-administrator, and the pioneering vision that has brought him worldwide respect and recognition through the Nobel Prize and in many other ways.

We are also fortunate that joining Dr. Watson as members of the initial staff of the Genome Research Office are two scientist-administrators from the National Institute of General Medical Sciences. Dr. Elke Jordan and Dr. Mark Guyer bring with them to the new office a wealth of ability and, in particular, broad experience in the administration of research in genetics.

Today we are activating another vital element of this important endeavor--the Program Advisory Committee on the Human Genome. The Committee's Charter, as approved by the Secretary of Health and Human Services, charges it to advise the NIH on all aspects of research in the area of genomic analysis. The Committee is expected to recommend initiatives that will promote the development of new technologies that will facilitate the acquisition, interpretation, analysis, and distribution of genetic and physical mapping information and DNA sequence data. The Committee is also expected to advise on research directions and identify areas of research requiring additional effort and to address the training needs of the research community, as they pertain to genomic analysis.

Because of the intense congressional interest in the human genome project we have been directed to report by early 1990 what we consider to be optimal strategy for the mapping and sequencing of the human genome. We look upon the Advisory Committee as a prime resource for the preparation of this crucial plan of action.

As you probably have guessed from the paper work to which you have been subjected thus far, the establishment of an advisory committee is not an action taken lightly by the Federal Government. Even though some of the formal appointment procedures have not been completed for all of the committee members, I take this opportunity to welcome you into the NIH family. I also wish to express personally, and on behalf of NIH, our deep appreciation for your willingness to share your time and your expertise in the interest of carrying out an exciting task which will lead to incalculable benefits over time.





REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

It is my pleasure to speak on behalf of the National Institutes of Health and to add an official word of welcome to the Fifth International Symposium on Cancer Research and AIDS. I will also take this occasion to express personally, and for the National Institutes of Health, our appreciation to the leading scientists from many different countries who have come to Venice to exchange their special insights on cancer and AIDS and to participate in discussions regarding them.

This symposium appropriately is the first official event of 1989's European Year Against Cancer, but its significance is not limited to any one continent or geographical area. It is an example of the gains to be realized from joining in cooperation across national borders and across organizational boundaries. For knowledge about cancer and AIDS has no national or organizational identity. Our best hope for progress in dealing with these scourges lies in continuous sharing of information and effort among all who perform research against them.

Currently in the United States there is serious discussion as to national priorities with respect to such major "big science" projects as the "super-collider" and the space station. The discussion has recently been enlarged to include such topics as the NIH initiative with respect to the mapping and sequencing the human genome. But there is a basic characteristic of the genome project that differs from the nature of such scientific ventures as the "super collider," and that difference is pertinent to the subjects of this symposium. Even though the genome

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\*Presented at the opening session of the Fifth International Symposium on Cancer Research and AIDS, European School of Oncology, Venice, Italy, January 11, 1989.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

project could involve expenditures of as much as \$3 billion over 15 years, there is no requirement for initial investment of an amount approaching a major fraction of the total cost. Thus the project need not be held in abeyance pending the expenditure of massive sums for essential equipment.

Another difference lies in the fact that it will not be necessary for the work to be done in one geographical location. Vital contributions to this effort will be made by government researchers in a number of different countries, by scientists working in academic institutions wherever situated, and in a variety of institutions including private, non-profit laboratories. Effective communication among the widespread centers of activity, however, is an absolute necessity for the success of such an effort.

The current discussions on the genome initiative bring to mind the beginnings of the national and international campaigns against cancer and AIDS. As each of these efforts has progressed it has involved a broader segment of the scientific community, the government, and the public, although not necessarily in that order. For example, in the United States, the so-called "War on Cancer" was initiated by a substantial increase in the amount of funds provided by the Federal Government through the National Cancer Institute. But the impetus for this step came from the intervention of a group of private individuals reinforced by the nationwide efforts of a voluntary organization, the American Cancer Society.

After the appropriation for the National Cancer Institute was doubled in the two-year period between 1970 and 1972, the additional funds were used, in part, to develop within academic and health care institutions new centers throughout the country. These centers were set up to conduct research and to communicate through demonstration and by other means improvements in the measures for preventing and treating cancer. Subsequently, new private, non-profit institutions for cancer research and treatment have been organized, in some instances adjacent to or affiliated with the existing cancer centers. Together the federally supported and the privately supported centers are instrumental in adding greatly to the resources of knowledge about the causes and nature of cancer, and have been highly

effective in increasing the numbers of physicians trained and experienced in its treatment.

While our efforts against AIDS have taken place within a different set of circumstances and on a compressed schedule, there are many similarities with the cancer effort in the way the program has developed. Furthermore, it is clear that no component of the informal consortium of the government, academia, private non-profit laboratories, and the interested public organizations can be spared if our efforts are to be as effective as the situation demands.

In the well planned sessions that are to follow we will hear authoritative presentations on important advances in our understanding of cancer and AIDS. It is fortunate indeed that such an array of different talents has been brought together to concentrate on issues so important to the health of people everywhere. In such a distinguished company the general discussions that are to follow the presentations will inevitably open new insights and raise new questions.

Furthermore, in addition to what we will gain from the discussions of the many topics on the formal agenda I think all of us can learn important lessons from some of the activities of Jacques Crozemarie and Umberto Veronesi. I am speaking of their successful efforts in reaching out to the medical community and the general public through various media and with useful information about the cause and prevention of cancer, and particularly of the enthusiasm with which they have been able to recruit supporters and co-workers for our common cause. The significance of their efforts can hardly be overstated. Judging from our experience in the United States, I can tell you that ultimately the cancer and AIDS programs of the Federal Government, of academia, and of private non-profit organizations are dependent upon the active understanding of the public.

Within a few weeks officials of the National Institutes of Health will appear before the Appropriations Committees of the U.S. Congress. We have every reason to believe that we will have an interested and sympathetic hearing from the Members of the committees. Over the years, even when--as



now--every effort is being made to curtail the budgets of Federal programs, the NIH has been given favorable treatment. In part this reflects unusual insight and vision on the part of leaders who have championed our cause, but it also is a result of the educational efforts of thousands of volunteers whose deep interest in disease problems, such as cancer, prompts them to call upon the government, academia, foundations, and sources of private wealth to carry the fight through research. The efforts and appeals of such "grassroots" organizations as the American Cancer Society cannot be ignored by the Members of Congress, who must always be sensitive to the people they represent, and this is particularly true of the Senators and Representatives who make up our cognizant committees.

In the United States we speak often of the value of "pluralism" in health related research programs--of the participation by government and private interests in such activities, each adding an indispensable and complementary element in this joint enterprise.

This pluralism--extended internationally--is an underlying theme of this symposium and is at the heart of the efforts in which we all are involved against cancer and AIDS. For this joint approach to succeed we must learn from each other, and through searching discussion share as well as add to our resources of knowledge. Such is the purpose of this symposium.

ESTABLISHMENT OF THE NATIONAL INSTITUTE ON DEAFNESS  
AND OTHER COMMUNICATION DISORDERS  
JAMES B. WYNGAARDEN, M.D.

INTRODUCTION

- O I AM PLEASED TO REPORT ON THE ESTABLISHMENT AND OPERATION OF THE NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS.
- O AS YOU KNOW, ON OCTOBER 28, 1988, THE PRESIDENT SIGNED INTO LAW, P.L. 100-553, THE NATIONAL DEAFNESS AND OTHER COMMUNICATION DISORDERS ACT OF 1988, THAT AUTHORIZES THE ESTABLISHMENT OF THE NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS (NIDCD).
- O THE GENERAL PURPOSE OF THE ACT IS STATED TO INCLUDE "THE CONDUCT AND SUPPORT OF RESEARCH AND TRAINING, THE DISSEMINATION OF HEALTH INFORMATION, AND OTHER PROGRAMS WITH RESPECT TO DISORDERS OF HEARING AND OTHER COMMUNICATION PROCESSES, INCLUDING DISEASES AFFECTING HEARING, BALANCE, VOICE, SPEECH, LANGUAGE, TASTE, AND SMELL."
- O IN CARRYING OUT THE PURPOSES OF THE ACT, THE INSTITUTE IS DIRECTED SPECIFICALLY TO:
  - OO ESTABLISH THE NATIONAL DEAFNESS AND OTHER COMMUNICATION DISORDERS ADVISORY BOARD;

- 00 PREPARE A PLAN TO INITIATE, EXPAND, INTENSIFY, AND  
COORDINATE ACTIVITIES OF THE INSTITUTE;
- 00 PROVIDE FOR THE DEVELOPMENT, MODERNIZATION, AND  
OPERATION OF MULTIPURPOSE CENTERS FOR DEAFNESS AND  
OTHER COMMUNICATION CENTERS; AND
- 00 ESTABLISH A DATA SYSTEM FOR THE COLLECTION, STORAGE,  
AND DISSEMINATION OF DATA DERIVED FROM PATIENT  
POPULATIONS.
- 00 ESTABLISH AN INFORMATION CLEARINGHOUSE FOR  
DISSEMINATION OF HEALTH INFORMATION TO THE PUBLIC.

#### ACCOMPLISHMENTS

- 0 IN THE SHORT TIME SINCE ENACTMENT OF THE ACT, A HOST OF  
ACTIVITIES HAVE BEEN UNDERTAKEN TO ESTABLISH AND OPERATE THE  
NEW INSTITUTE.
- 0 DR. JAY MOSKOWITZ, ASSOCIATE DIRECTOR FOR SCIENCE POLICY AND  
LEGISLATION, NIH, HAS BEEN APPOINTED ACTING DIRECTOR OF THE  
NIDCD.

- 0 AN ORGANIZATIONAL CHANGE PACKAGE HAS BEEN DEVELOPED TO OFFICIALLY ESTABLISH THE NEW INSTITUTE AND, THEREBY, PROVIDE THE LEGAL BASIS FOR FORMALLY IMPLEMENTING THE PROVISIONS OF THE ACT REQUIRING THE TRANSFER OF RESOURCES AND PERSONNEL FROM THE NINCDS TO THE NIDCD.
- 0 A SEARCH PLAN HAS BEEN DEVELOPED TO GUIDE A NATIONAL CAMPAIGN TO SELECT THE FIRST PERMANENT DIRECTOR OF THE NIDCD. ADVERTISEMENTS WILL BE IN THE FEBRUARY ISSUES OF JOURNALS AND NEWSLETTERS SUCH AS SCIENCE AND CHRONICAL OF HIGHER EDUCATION.
- 0 NOMINATIONS WERE SOUGHT AND HAVE BEEN RECEIVED IN GREAT NUMBERS FOR APPOINTMENT OF MEMBERS TO THE ADVISORY BOARD AND ADVISORY COUNCIL OF THE NEW INSTITUTE. THE ENTHUSIASTIC RESPONSE FROM RELEVANT SCIENTIFIC, PROFESSIONAL, AND LAY COMMUNITIES PROVIDES A STRONG SLATE OF CANDIDATES FROM WHICH TO SELECT MEMBERS FOR THESE IMPORTANT ADVISORY COMMITTEES. THE ADVISORY COUNCIL WILL BE PATTERNED ALONG TRADITIONAL LINES.
- 0 GUIDED BY THE REPORTS OF BOTH THE HOUSE AND SENATE AUTHORIZING COMMITTEES, PROGRAMS IN DEAFNESS AND OTHER COMMUNICATION DISORDERS TOTALING \$86,576,000 HAVE BEEN IDENTIFIED FOR TRANSFER FROM THE NINCDS TO THE NEW



INSTITUTE, PENDING THE SECRETARY'S APPROVAL, INCLUDING \$2,964,000 FOR ADMINISTRATIVE EXPENSES.

- 0 THE SCIENTIFIC PROGRAMS TO BE TRANSFERRED WHEN THE PLAN IS APPROVED INCLUDE BASIC AND CLINICAL RESEARCH IN AREAS MENTIONED IN THE ACT: DISORDERS OF HEARING AND BALANCE, DISORDERS OF VOICE AND SPEECH, AND SENSORY DISORDERS AFFECTING TASTE, TOUCH, AND SMELL. EMPHASIS WILL ALSO BE GIVEN TO RESEARCH CAREER DEVELOPMENT AND RESEARCH TRAINING IN THE DISCIPLINES RELEVANT TO THESE AREAS. FINALLY, ALL ELEMENTS OF THE EXISTING NINCDS INTRAMURAL PROGRAM ASSOCIATED WITH RESEARCH ON HEARING AND SPEECH DISORDERS WILL BE TRANSFERRED TO THE NIDCD.
  
- 0 THE SPECIFIC PROGRAM ELEMENTS THAT HAVE BEEN IDENTIFIED FOR TRANSFER INCLUDE:
  - 00 RESEARCH PROJECT GRANTS. TWO HUNDRED AND FORTY-TWO (242) FY 1989 NONCOMPETING CONTINUATION RESEARCH PROJECT GRANTS ARE BEING TRANSFERRED TO THE NIDCD, TOGETHER WITH \$51,164,000 FOR THEIR SUPPORT. AN ADDITIONAL \$16,286,000 WILL BE TRANSFERRED TO SUPPORT 90 NEW AND COMPETING RENEWAL GRANTS. THIS REPRESENTS A PRO RATA SHARE OF THE 655 COMPETING GRANTS APPROPRIATED TO THE NINCDS FOR 1989, BASED ON THE NIDCD PROPORTION OF NONCOMPETING GRANTS.

- 00 RESEARCH CENTERS. A TOTAL OF \$7,552,000 IS SCHEDULED FOR TRANSFER TO THE NIDCD FOR CLINICAL RESEARCH CENTERS. THESE FUNDS ARE SUFFICIENT TO FUND NINE RESEARCH CENTERS. SEVEN NONCOMPETING CONTINUATION CENTERS ARE BEING TRANSFERRED WITH \$5,981,000; \$1,571,000 IS AVAILABLE TO FUND TWO COMPETING CENTERS.
- 00 OTHER RESEARCH GRANTS. \$2,300,000 IS BEING TRANSFERRED FOR OTHER RESEARCH GRANTS. THIS TRANSFER INCLUDES \$1,973,000 FOR 30 CONTINUATION PROJECTS, AS FOLLOWS: 27 RESEARCH CAREER PROGRAM GRANTS FOR \$1,698,000; A CONFERENCE GRANT FOR \$25,000; AND TWO SCIENTIFIC EVALUATION GRANTS FOR \$250,000. AN ADDITIONAL \$327,000 IS AVAILABLE FOR AN ESTIMATED SIX ADDITIONAL OTHER RESEARCH GRANTS.
- 00 RESEARCH TRAINING (NRSA). \$2,273,000 IS BEING TRANSFERRED TO SUPPORT 96 FULL-TIME TRAINING POSITIONS. OF THIS AMOUNT, \$214,000 WILL BE REQUIRED TO SUPPORT EIGHT NONCOMPETING CONTINUATION INDIVIDUAL FELLOWSHIPS, AND \$1,581,000 TO SUPPORT NONCOMPETING INSTITUTIONAL TRAINING GRANTS. \$478,000 REMAINS FOR FUNDING OF COMPETING AWARDS.

- 00 RESEARCH AND DEVELOPMENT CONTRACTS. \$1,087,000 IS BEING TRANSFERRED TO THE NIDCD TO SUPPORT UP TO FOUR CONTRACTS FOR THE DEVELOPMENT OF AUDITORY PROSTHESES. THE CURRENT ESTIMATE FOR THESE CONTRACTS IS \$1,048,000. THESE FUNDS WILL SUPPORT STUDIES INVOLVING THE HISTOPATHOLOGY ASSOCIATED WITH COCHLEAR IMPLANTS, THE DEVELOPMENT OF SPEECH PROCESSORS FOR AUDITORY PROSTHESES, AND THE DETERMINATION OF THE FEASIBILITY OF A CENTRAL NERVOUS SYSTEM AUDITORY PROSTHESIS.
- 00 INTRAMURAL RESEARCH. SEVENTEEN FULL-TIME EQUIVALENT POSITIONS HAVE BEEN TRANSFERRED TO THE NIDCD, TOGETHER WITH \$2,174,000 TO SUPPORT SALARIES, EQUIPMENT, SUPPLIES, AND CENTRAL SERVICES FOR THESE STAFF MEMBERS. TRANSFERS WILL INCLUDE THE ENTIRE LABORATORY OF NEURO-OTOLARYNGOLOGY, THE AUDIOLOGY UNIT, AND THE SPEECH PATHOLOGY UNIT.
- 00 RESEARCH MANAGEMENT AND SUPPORT. THIRTEEN FULL-TIME EQUIVALENT POSITIONS ARE BEING TRANSFERRED TO THE NIDCD, TOGETHER WITH \$776,000 TO SUPPORT SALARIES, EQUIPMENT, SUPPLIES AND CENTRAL SERVICES FOR THESE STAFF MEMBERS. THIS TRANSFER WILL INCLUDE THE STAFF OF THE DIVISION OF COMMUNICATIVE AND NEUROSENSORY DISORDERS OF THE NINCDS, TOGETHER WITH ALL STAFF IN

GRANTS MANAGEMENT AND SCIENTIFIC REVIEW THAT CURRENTLY SUPPORT THE ACTIVITIES OF THAT DIVISION.

- 00 ADMINISTRATIVE COSTS FOR ESTABLISHMENT OF THE INSTITUTE. IN THE NINCDS APPROPRIATION FOR 1989, THE CONGRESS INCLUDED \$3,000,000 IN START-UP COSTS FOR THE NIDCD. THIS \$3,000,000 IS TRANSFERRED TO THE NIDCD, LESS THE 1.2 PERCENT REDUCTION THAT WAS APPLIED TO ALL ACCOUNTS IN THE 1989 LABOR-HHS-EDUCATION APPROPRIATIONS ACT. THE TOTAL ADD-ON FUNDS TO BE TRANSFERRED AMOUNT TO \$2,964,000.
- 0 ADDITIONAL EXTRAMURAL RESEARCH GRANT PROGRAMS TOTALING \$8,497,000 THAT HAVE APPLICATION TO EITHER NINCDS OR NIDCD ARE BEING EXAMINED TO DETERMINE THEIR MOST APPROPRIATE ORGANIZATIONAL LOCATION.
- 0 THE CONFERENCE REPORT FOR THE FY 1989 LABOR-HHS-EDUCATION APPROPRIATIONS BILL REQUESTED THAT "THE SECRETARY REPORT TO THE CONGRESS ON A QUARTERLY BASIS DURING FY 1989 CONCERNING THE ESTABLISHMENT AND OPERATION OF THE NEW INSTITUTE, BEGINNING ON DECEMBER 31, 1988."
- 0 AS MANY OF YOU ARE AWARE, A TASK FORCE COMPRISED OF PANELS OF OUTSIDE EXPERTS WAS ESTABLISHED TO ASSIST THE INSTITUTE IN PREPARING A NATIONAL RESEARCH STRATEGY FOR DEAFNESS AND



OTHER COMMUNICATION DISORDERS. THE TASK FORCE, UNDER THE CO-CHAIRMANSHIP OF DR. CHARLES BERLIN OF THE KRESGE HEARING RESEARCH LABORATORY AND DR. ROBERT RUBEN OF MONTEFIORE MEDICAL CENTER, MET ON JANUARY 17-19, 1989.

00 TO ASSESS THE STATE OF KNOWLEDGE IN EACH OF THE MAJOR REAS OF RESEARCH WITHIN THE PURVIEW OF THE NEW INSTITUTE.

00 TO IDENTIFY EMERGING RESEARCH OPPORTUNITIES, AND

00 TO DEVELOP A NATIONAL STRATEGY TO GUIDE ACTIVITIES IN DEAFNESS AND OTHER COMMUNICATIVE DISORDERS.

0 THE VIEWS AND COMMENTS OF A BROAD SEGMENT OF THE DEAFNESS AND OTHER COMMUNICATION DISORDERS COMMUNITY WILL BE SOLICITED ON A DRAFT OF THE REPORT BEFORE PRESENTING IT AT THE SPRING MEETINGS OF THE NIDCD ADVISORY COUNCIL AND ADVISORY BOARD.

### CONCLUSION

0 ENCOURAGED BY THE SUCCESS THAT THE NATIONAL EYE INSTITUTE HAS ACHIEVED SINCE ITS INCEPTION 20 YEARS AGO, MANY VIEW THE ESTABLISHMENT OF THE NIDCD AS THE BEGINNING OF A NEW ERA IN CONFRONTING DEAFNESS AND OTHER COMMUNICATION DISORDERS.

00 ONLY TIME WILL REVEAL THE DEGREE TO WHICH THIS HOPE CAN  
BE REALIZED; BUT THE CREATION OF THE NEW INSTITUTE  
DOES, INDEED, OCCUR AT A PROPITIOUS TIME IN VIEW OF THE  
DRAMATIC DEVELOPMENTS OCCURRING IN SUCH UNDERLYING  
AREAS OF SCIENCE AS MOLECULAR BIOLOGY, GENETICS, AND  
NEUROBIOLOGY THAT HOLD PROMISE OF REVOLUTIONIZING THE  
APPROACH TO THE STUDY OF DEAFNESS AND OTHER  
COMMUNICATION DISORDERS.

0 A GOOD START HAS BEEN MADE IN ESTABLISHING THE NEW INSTITUTE  
AND SENDING IT ON ITS PATH, BUT MUCH REMAINS TO BE DONE.  
THE NIH LOOKS FORWARD TO WORKING CLOSELY WITH THE LEADERSHIP  
OF THE VARIOUS PROFESSIONAL SOCIETIES, VOLUNTARY HEALTH  
ORGANIZATIONS, AND THE CONGRESS IN IMPLEMENTING THE  
PROVISIONS OF THE ACT AND ACHIEVING THE INTENT OF THOSE WHO  
WORKED DILIGENTLY TO ESTABLISH THE NEW INSTITUTE.



TALKING POINTS\*

BY

JAMES B. WYNGAARDEN\*\*

III. HUMAN GENE THERAPY STATUS REPORT

O ON JANUARY 19, I ACCEPTED THE RECOMMENDATION OF THE RAC AND THEREBY APPROVED THE PROPOSAL FOR THE HUMAN GENE THERAPY STUDY BY DRS. ANDERSON, ROSENBERG AND BLAESE. I BELIEVE THAT OUR REVIEW HAS BEEN THOROUGH AND OUR DECISION IS IN THE PUBLIC INTEREST.

O AS YOU KNOW, THE REVIEW PROCESS TOOK SEVEN MONTHS. I DO NOT THINK THAT TIMEFRAME TOO LONG, GIVEN THE IMPORTANCE OF THE ISSUE.

O I WOULD LIKE TO REVIEW THE PROCESS THAT CULMINATED IN MY APPROVAL.

O THE PROPOSAL WAS FIRST RECEIVED IN JUNE AND JULY 1988 BY A NUMBER OF INTERNAL NIH REVIEW COMMITTEES CHARGED WITH OVERSIGHT OF PROPOSED EXPERIMENTS. ONE OF THE KEY ELEMENTS OF THEIR REVIEW IS SAFETY--NOT ONLY THE SAFETY OF THE PATIENTS INVOLVED, BUT OF ALSO THE INVOLVED INVESTIGATORS AND HEALTH CARE PERSONNEL. THE CONCERN FOR SAFETY EXTENDS AS WELL TO THE PUBLIC HEALTH AND TO THE ENVIRONMENT.

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\*PRESENTED AT THE MEETING OF THE NIH RECOMBINANT DNA ADVISORY COMMITTEE, JANUARY 30, 1989, BETHESDA, MARYLAND.

\*\*DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND.



O THE INSTITUTIONAL REVIEW BOARDS OF THE TWO SPONSORING INSTITUTES AND THE NIH INSTITUTIONAL BIOSAFETY COMMITTEE ALL GAVE "CONDITIONAL APPROVAL" WITH CERTAIN STIPULATIONS.

O AMONG THESE STIPULATIONS WAS A REQUIREMENT THAT THE RECOMBINANT DNA ADVISORY COMMITTEE GRANT ITS APPROVAL OF THE PROPOSED PROJECT.

O ON JULY 29, 1988, THE HUMAN GENE THERAPY SUBCOMMITTEE OF THE RAC MET TO CONSIDER THE GENE TRANSFER PROPOSAL. THEY DEFERRED APPROVAL PENDING RECEIPT OF ADDITIONAL DATA. THE SUBCOMMITTEE PREPARED SPECIFIC QUESTIONS TO BE ANSWERED BY THE SCIENTISTS PRIOR TO THE OCTOBER 3, 1988, RAC MEETING.

O THE SUBCOMMITTEE MET VIA TELEPHONE CONFERENCE ON SEPTEMBER 29, 1988. IT WAS THE UNANIMOUS DECISION OF THE SUBCOMMITTEE MEMBERS AND CONSULTANTS PARTICIPATING IN THE CONFERENCE THAT THE QUESTIONS POSED AT THE JULY 29, 1988, MEETING HAD NOT YET BEEN ANSWERED BY THE DATA PROVIDED TO DATE. THUS, THE SUBCOMMITTEE AGREED TO DEFER APPROVAL OF THE PROPOSAL.

O ON OCTOBER 3, 1988, THE RAC RECEIVED DATA NOT PREVIOUSLY SUBMITTED TO THE HUMAN GENE THERAPY SUBCOMMITTEE. BASED ON THESE DATA, THE RAC RECOMMENDED APPROVAL OF THE PROTOCOL, BY A VOTE OF 16 IN FAVOR, 5 OPPOSED, AND NO ABSTENTIONS.

O BECAUSE CERTAIN CONCERNS RAISED BY TECHNICAL EXPERTS OF THE HUMAN GENE THERAPY SUBCOMMITTEE HAD NOT YET BEEN RESOLVED, I REQUESTED THAT THE ENTIRE PROTOCOL, INCLUDING DATA PRESENTED AT THE OCTOBER 3 RAC

MEETING AND ANY ADDITIONAL DATA OBTAINED SINCE THAT DATE, BE REVIEWED BY THE SUBCOMMITTEE AT ITS DECEMBER 9, 1988, MEETING.

O I STRONGLY BELIEVED THAT ALL THE DATA SHOULD COME BEFORE ALL OF THE GROUPS INVOLVED IN REVIEW, PARTICULARLY BECAUSE THEY ARE CONSTITUTED WITH EXPERTS IN VARIOUS FIELDS AND WITH VARIED PERSPECTIVES THAT NEED TO BE BROUGHT TO BEAR IN CONSIDERING A MATTER OF SUCH GREAT IMPORT. THE PUBLIC IS OWED NOTHING LESS FROM ITS GOVERNMENT.

O I MIGHT ADD THAT WE ARE VERY AWARE OF THE NEED AND DESIRABILITY OF CONDUCTING SUCH BUSINESS IN PUBLIC SESSION. NIH HAS TAKEN THIS STANCE, MOST PARTICULARLY RELATING TO DNA RECOMBINANT MATTERS, SINCE THE VERY FIRST MEETINGS WE HELD ON THIS THEN "NEW SCIENCE" BACK IN 1974, FOLLOWING ASILOMAR. AS YOU ALL KNOW, THE MEETINGS OF THE RAC AND ITS SUBCOMMITTEE ON HUMAN GENE THERAPY HAVE ALL BEEN DULY ANNOUNCED IN THE FEDERAL REGISTER AS WELL AS THROUGH INTERACTION WITH THE NEWS MEDIA. IN FACT, AS YOU ARE ALL AWARE, OUR REVIEW OF THIS PARTICULAR RESEARCH PROPOSAL HAS BEEN DESCRIBED IN A NUMBER OF WIDELY-CIRCULATED NEWS MEDIA OVER THE COURSE OF SEVERAL MONTHS.

O AN AGGREGATE OF PERSPECTIVES AND EXPERTISE, AS I MENTIONED EARLIER, WAS APPLIED IN THE REVIEW OF THIS PROTOCOL. MY REQUEST WAS CARRIED OUT--THE HUMAN GENE THERAPY SUBCOMMITTEE REVIEWED THE ADDITIONAL DATA PROVIDED TO THE RAC FOR ITS OCTOBER 3 MEETING. THE HUMAN GENE THERAPY SUBCOMMITTEE VOTED UNANIMOUSLY TO APPROVE THE PROTOCOL. IN ADDITION, THE TWO NIH INSTITUTIONAL REVIEW BOARDS HAVE GRANTED THEIR APPROVAL, AS HAVE THE

NIH INSTITUTIONAL BIOSAFETY COMMITTEE AND THE FDA VACCINES AND RELATED BIOLOGIC PRODUCTS ADVISORY COMMITTEE.

O WHEN THESE DECISIONS WERE REACHED, A FORMAL MAIL BALLOT WAS DISTRIBUTED TO RAC MEMBERS, INCLUDING THE MOTION APPROVED BY THE HUMAN GENE THERAPY SUBCOMMITTEE AND THE MINUTES OF THEIR DECEMBER 9, 1988, MEETING. BECAUSE THERE HAD BEEN NO SUBSTANTIVE CHANGE IN EITHER THE PROPOSAL OR THE MOTION APPROVED BY THE RAC PREVIOUSLY, I DID NOT ASK RAC MEMBERS FOR FURTHER DELIBERATION. THE PURPOSE OF THE MAIL BALLOT WAS TO PROVIDE A FINAL, FORMAL RECORD OF THE ENTIRE REVIEW PROCESS.

O ON DECEMBER 9, THE HUMAN GENE THERAPY SUBCOMMITTEE APPROVED THE SAME MOTION VOTED BY THE RAC ON OCTOBER 3, CHOOSING TO ADD A FOURTH POINT, A POINT OF CLARIFICATION DERIVED FROM PRIOR RAC DELIBERATIONS. THUS, THE MOTION ON THE MAIL BALLOT SENT TO MEMBERS OF THE RAC WAS AS FOLLOWS: TO APPROVE THE HUMAN GENE THERAPY PROPOSAL SUBMITTED BY DRS. ANDERSON, BLAESE, AND ROSENBERG WITH THE FOLLOWING STIPULATIONS:

1. THERE WILL BE NO MORE THAN 10 PATIENTS IN THE INITIAL TRIALS.
2. THE PATIENTS SELECTED WILL HAVE A LIFE EXPECTANCY OF ABOUT 90 DAYS.
3. THE PATIENTS WILL HAVE GIVEN FULLY INFORMED CONSENT TO PARTICIPATE IN THE TRIAL.
4. THE INVESTIGATORS WILL PROVIDE ADDITIONAL DATA BEFORE EXPANDING THE TRIAL BY ADDING PATIENTS OR BY INSERTING A GENE FOR THERAPEUTIC PURPOSES.

0 THROUGH THIS PROCESS OF REVIEW, THE INVESTIGATORS HAVE DEMONSTRATED TO THE SATISFACTION OF THE REVIEW COMMITTEE THAT THE USE OF AMPHOTROPICALLY PACKAGED RETROVIRAL VECTORS DOES NOT APPEAR TO POSE A PUBLIC HEALTH RISK TO PATIENTS OR TO HEALTH CARE PERSONNEL, EVEN IN THE EVENT OF ACCIDENTAL EXPOSURE TO EXPERIMENTAL MATERIAL.

0 I ACCEPTED THE RECOMMENDATION BROUGHT BEFORE ME AND FULLY ENDORSE THE START OF THIS IMPORTANT, LANDMARK RESEARCH PROJECT. THE DETAILED REVIEW PROCEDURE, THE OBVIOUS EXPERTISE AND COMMITMENT OF THE VARIOUS MEMBERS OF THE COMMITTEES INVOLVED, AND THE FULL AND OPEN DISCUSSION WE HAVE HAD CONVINCE ME THAT THIS PROTOCOL DOES NOT PRESENT A RISK TO PUBLIC HEALTH OR TO THE ENVIRONMENT.



PART 2 OF TALKING POINTS FOR DR. WYNGAARDEN FOR THE RAC MEETING

JANUARY 30, 1989

IV. PROPOSAL TO RECOMMEND AMENDING THE RECOMBINANT DNA ADVISORY  
COMMITTEE CHARTER.

O YOU HAVE ALL HEARD MY RECAPITULATION OF THE REVIEW PROCESS WE  
FOLLOWED FOR THE HUMAN GENE TRANSFER PROPOSAL.

O IT SEEMS TO ME THAT IN ORDER TO ASSURE A MORE LOGICAL, STEP-WISE FLOW  
OF DECISION MAKING IN THE FUTURE, IT MIGHT BE USEFUL TO CODIFY, IN SOME  
WAY, THE PROCESS. I HAVE DISCUSSED THIS WITH THE CHAIRMAN OF THE RAC  
AND THE ACTING EXECUTIVE SECRETARY AND THEY AGREE.

O THIS COULD NOT BE DONE THROUGH A REVISION OF THE RECOMBINANT DNA  
GUIDELINES BECAUSE THE GUIDELINES DO NOT DISCUSS THE REVIEW PROCESS AT  
THIS LEVEL OF DETAIL. A BETTER WAY TO ACCOMPLISH THAT WOULD BE BY MEANS  
OF A CHANGE IN THE CHARTER OF THE RAC.

O BECAUSE THE RAC CHARTER IS A DOCUMENT SIGNED BY THE SECRETARY OF HHS,  
THE PROPER BUREAUCRATIC ACTION WOULD BE FOR ME TO MAKE A RECOMMENDATION  
TO THE HHS SECRETARY THAT SUCH A CHANGE BE INCORPORATED INTO THE RAC  
CHARTER.

O I WOULD LIKE THE HELP OF THE RAC IN FRAMING SUCH A RECOMMENDATION TO  
THE SECRETARY.

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O A PROPOSAL OF SUCH AN AMENDMENT IS BEFORE YOU ON PAGE 3 OF MAILING 1. IT READS: "ALL PROPOSALS REFERRED TO A SUBCOMMITTEE FOR FORMAL REVIEW MUST BE APPROVED BY A MAJORITY OF SUBCOMMITTEE MEMBERS BEFORE BEING SUBMITTED TO THE PARENT COMMITTEE. IF A PROPOSAL IS REJECTED BY A SUBCOMMITTEE, THE INVESTIGATOR MAY APPEAL THIS DECISION BY APPLICATION TO THE DIRECTOR, NIH."

O I WOULD LIKE THE MEMBERS OF THE RAC TO CONSIDER AND DISCUSS THIS PROPOSAL.



TALKING POINTS\*  
BY  
JAMES B. WYNGAARDEN, M.D.\*\*

Issues Facing Biomedical Science in the Next Few Years

On such as this anniversary it is fitting to look backward to assess how far we've come and to look forward to try to see the way ahead.

In a brief time with you today, I would like to share some of my thoughts as NIH Director about the major issues facing biomedical science now and in the next few years.

BUDGET CONSIDERATIONS

It is not uncommon in recent years for university officials, presidents of professional societies, heads of voluntary health agencies and others to proclaim that "the sky is falling", that the NIH appropriation has been slashed, that federal support of biomedical research is capricious, and the future uncertain.

I am impressed that the opposite is true.

The indiscriminate gloomy assessments of federal funding trouble me, because they do not describe accurately the current state of affairs. Comments of this nature generate unnecessary pessimism.

My optimism is based on the achievements of successive generations of strong champions of biomedical research in the executive branch, and in Congress--encouraged and guided by the advocacy of voluntary health organizations, professional and academic societies, and individuals.

The past seven years (82-89) have seen a period of sustained growth of the total appropriation for the NIH, amounting to 96 percent in current dollars and 35 percent in real terms. This growth has erased the 14 percent loss in purchasing power experienced by NIH from FY 1979 through 1982. In each of the last four years, the NIH appropriation has reached a new high in constant dollar terms.

- o 3.6 - 7.2
- o 5% /Yr.
- o Biomedical deflated

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\*Address for the Sigma Xi, University of Miami School of Medicine, Miami, Florida, March 2, 1989.

\*\*Director, National Institutes of Health, Bethesda, Maryland.



The overall growth rate of the NIH appropriations since the late 1960s has been nearly 3 percent per year, even factoring in the three brief intervals when the appropriation lost purchasing power. In only two years out of the past 30 did the appropriation in current dollars decline from that of the previous year. (In all other years when purchasing power was lost, the explanation was inflation running ahead of appropriation.)

Some leaders in the scientific and academic communities saw this brief recession as "the beginning of the end of federal support for biomedical research", but since that time the NIH appropriation has increased more than fourfold.

The President's 1990 budget--which I will defend before the House and the Senate in the next few months--is \$7.5 billion, an increase of 5.3 percent over the FY 1989 budget. After ruling out the effects of inflation, the budget is essentially stable.

- o 25% AIDS
- o 3.7% Other

The important point, however, is how much excellent research that budget can support. One way of looking at this is to consider the award rates--that is the percentage of approved grant applications we are able to fund. In the nearly seven years that I have been Director, the overall award rates have been about even--in 1982 34.7 percent and in 1988 35.4 percent. It is true that back in 1975, we were able to fund about 60 percent of grants eligible for award. The difference is the increased competition (i.e., we are receiving more grant applications) and the increased cost of the average grant.

Thus, we are holding at about 35-39 percent. More problematic is the fact that some of the institutes are considerably lower than the NIH overall average.

- o Research project grants:
  - 72 - 9691
  - 73 - 9383
  - 74 - 11014
  - 82 - 15970
  - 88 - 20,202
  - 89 - 20,731

## TRAINING

Training is a major, long-standing concern for the biomedical research community because we know how important the quality and quantity of our research trainees of today will be for science in the future. This is especially true as biomedical research becomes more complex and intellectually demanding.

Over the years, NIH has been able to support approximately the number of trainees projected by the National Academy of Sciences. About 10,000 per year.

This year, we have decided that it is necessary to raise stipends of (NRSA) trainees in order to attract and retain the best young people in our programs. This has meant that we will probably have to reduce the number of trainees supported. We are taking all feasible steps to ensure that the training grants for renewal in 1989 do not bear the full burden of the requisite reduction in the number of trainees.

The issue of training becomes even more acute when you consider the needs that will be generated by the burgeoning fields opened up through biotechnology, for example. Another major concern is training for the people who will manage and staff the growing number of necessary clinical trials, particularly in AIDS.

Indeed, the rapid expansion of this important activity suggests that we might well reexamine some of the premises on which we have developed and conducted our programs of research training for clinical investigators. Our research training programs have not been oriented specifically to carrying out clinical trials, where shortages will become acute.

#### MISCONDUCT IN SCIENCE

Although misconduct in science is a rare occurrence and the incidence does not appear to have increased, this is a critical issue that cannot be ignored.

The NIH has received approximately 15-20 serious allegations of misconduct each year since 1982. While these are unlikely to represent the full tally of episodes, it should be kept in mind that NIH funds approximately 28,000 projects per year and supports the work of approximately 52,000 scientists.

- o Darsee

Nonetheless, every instance of misconduct is serious. Misconduct in science erodes the fabric of science, interferes with intellectual pursuit, and sours the public and Congress who have been our supporters over the years.

- o Dingle/Wyden
- o Baltimore
- o Inspector General

The responsibility lies most heavily not on NIH but on individual institutions. For this reason, NIH recently published in the Federal Register a proposed rule on "Responsibilities of PHS Awardee and Applicant Institutions for Dealing with and Reporting Possible Misconduct in Science".

Under this proposed rule, an assurance system would be established requiring each grantee institution to have written policies and procedures in place for dealing with and reporting scientific misconduct that occurs within its own institution.

A key consideration in formulating the proposed rule has been defining scientific misconduct. It is important to address effectively instances of "errant" science while preserving investigators' ability to pursue scientific goals through novel, creative, but sound approaches.

Generally, we define misconduct as serious deviation, such as fabrication, falsification, or plagiarism, from accepted practices or failure to comply with regulations protecting human subjects or pertaining to the welfare of animals.

The proposed rule outlines the process to be followed in response to an allegation of misconduct, as well as reporting requirements. Two steps are: an inquiry (fact gathering to determine if an investigation is warranted) and an investigation.

Dealing properly with a serious allegation of misconduct is a critical responsibility of the institution, but preventing misconduct is even more crucial.

The Institute of Medicine, with funding from the NIH, recently made public a report on "integrity in science". That report placed a great deal of responsibility upon institutions to create environments where ethics and integrity can be maintained.

For example, the report suggested that universities and the federal agencies should limit the number of scholarly articles required for promotions, tenure or federal grants.

And that research institutions should establish rules to end the practice of "gift authorship".

And further that research institutions ensure that all science students receive formal training in responsible research practices.

(In 1986, Sigma Xi published its report, Honor in Science, aimed at educating young scientists on the responsible conduct of research.)

The IOM report included some specific suggestions for the NIH to consider. I commend that report to your attention.

o OSI/OSIR

#### TIES WITH INDUSTRY/CONFLICT OF INTEREST

Just in the past decade, new and productive modes of collaboration between industry and academic organizations have developed. Many universities have also helped to establish venture capital firms that can enter into



commercial relations with faculty researchers for the purpose of marketing products derived from university-based research. These commercial arrangements are becoming an important additional source of research funds for many universities.

- o Weiss - clinical trials-TIMI-stock options-consult
  - 1. disclosure
  - 2. roles

With intramural NIH, collaborative ventures have come much more recently--just in the past year or so--with the passage of the Technology Transfer Act which mandates NIH to engage in so-called CRADAs--collaborative research and development agreements with industry.

When the first university/industry collaborations came into being there was much concern--expressed in scientific circles and the scientific press--that such ties would destroy the very fabric of scientific intellectual pursuit, even corrupt the institution of free inquiry.

We have no evidence that this has happened, but there are issues to be concerned with:

Preservation of free and open discussion among scientists within an institution and with researchers at other institutions. This matter has caused some concern among NIH scientists who may either consult or collaborate with industry.

Conflict of interest. This is a particular concern with regard to clinical trials. On January 20 in the "Guide to Grants and Contracts", NIH announced plans to issue guidelines for investigators funded by extramural awards, and stated that we "expect that participating investigators and consultants will not have financial interests in organizations or entities that produce drugs, devices, or other inventions studied in a controlled clinical trials." (there will be some exemption for special cases.)

The AAMC is currently studying institutions' policies on conflict of interest in science with the expectation of producing a guidance document or model policy.

Skewing of the research agenda. This is a much more subtle, but important effect that industry relationships may have on an institution--NIH or an academic center. If ties with industry, for example, caused NIH to become overly geared toward commercialization to the detriment of strong support for basic research.

## ANIMALS IN RESEARCH

The use of animals in biomedical research will likely be a major item on the legislative agenda this year, in Congress and in state legislatures.

NIH's view is that for the foreseeable future, our biomedical research efforts require continued reliance on experimentation with animals.



Otherwise, our efforts to improve human health cannot be maintained or increased.

At the same time, NIH requires the humane care and proper treatment of animals in NIH-sponsored laboratory research.

For a number of years, federally supported laboratories have been the targets of break-ins; theft of animals; and destruction of property, equipment and valuable records. The NIH has been the site of a sit-in, prolonged picketing of 100 days, and two recent demonstrations by animal rights advocates.

More recently, activists who once operated under the guise of seeking proper treatment of animals in research have begun to show their true colors and focus on the worth of particular research projects rather than on care or housing of the animals. Their true goal is to stop all research involving animals. This anti-intellectual mindset is an incredibly destructive force in our society.

#### FACILITIES

A newly published report--done for NIH by the NSF--concerns the nationwide need for research facilities.

This survey concentrated only on biomedical research facilities, most of which (84 percent) are at academic institutions.

Among academic institutions, 50-54 percent described their current space as generally adequate in the medical sciences ("sufficient to support most research needs...but may have some limitations"). And 37-45 percent as inadequate ("not sufficient to support the needs of your research").

Needs were somewhat greater in the basic biological sciences, with 45-46 percent describing their space as generally adequate and 46-51 percent as inadequate.

The findings of the report are consistent with reports from institutions indicating that new construction is driven at least as much by needs to upgrade quality of their research facilities to meet emerging safety and other requirements such as new program areas as it is to expand their total amount of research space. Among the factors often cited as contributing to the increased costs of facilities construction were increasing standards for animal facilities, for toxic waste disposal, for biohazard control and for data capabilities.

We recognize that the issues related to funding research facilities are a shared responsibility of state, local, and federal governments, along with the private sector. Embedded in the context of federal fiscal constraints, there is no simple solution in sight.

But, we must keep this issue in sight, particularly in light of new scientific discoveries and new technologies that are changing the nature of research needs and requiring more sophisticated facilities.

#### PRIVATIZATION OF INTRAMURAL NIH

Many of you may have heard about suggestions for privatizing NIH, and I thought it might be useful to bring you up to date on that matter.

Last year a suggestion was made by the OMB for "the privatization of the intramural NIH research program". In typical Washington fashion, the suggestion took the form of a "trial balloon". That is, most of the higher echelons of NIH, the Congress, and the public learned about the idea reading the New York Times early one morning.

The idea was that in order to solve some of our problems in attracting and retaining the caliber of scientific investigators we need to maintain research excellence, and to achieve a degree of flexibility and control, NIH should be moved out of government and away from federal restrictions such as pay caps.

As some of you may know, NIH has a severe problem in that we are increasingly unable to compete with the Nation's medical schools, universities, and industry for senior scientists. In attempting to fill senior positions we are finding that many potential candidates do not wish to be considered, primarily because of the large gap between the pay and benefits they are receiving and the compensation NIH can offer.

I cannot think of anyone or any group that favored the idea of privatization. The Institute of Medicine called the idea of making the NIH intramural program free-standing and self-supporting "undesirable and impractical" and recommended higher salaries for NIH's top scientists and greater independence for the organization.

With the fall of the proposed pay raise for Congress and other federal workers (including NIH scientists) in mid-February, we are renewing our efforts to gain higher salaries for top scientists through a new pay scale called the Senior Biomedical Research Service.

#### MAPPING THE HUMAN GENOME

We are very enthusiastic about the very clear signals we have gotten from the Administration and the Congress for undertaking a systematic program to map and sequence the entire human genome.

Ultimately, we expect to advance to a determination of the complex sequence of the DNA of all the constituent genes. In addition to the enormous amounts of biomedical information and better understanding of the role of genes in human disease that will come from this effort, many important scientific and technological advances can be expected, having both basic and commercial applications.

In 1988, \$18 million was allocated to this effort, and in 1989, Congress appropriated \$27.6 million for the genome program. The President's budget for 1990 requests \$100 million.

Organizing this worldwide effort--which is expected to cost approximately \$3 billion over the next 15-20 years--is a major challenge. Questions include:

which organisms in addition to man should be studied? how can we train the scientists needed for this long-term effort? do we need special research centers devoted to aspects of the program. if so, how should they be organized? what are the legal and ethical issues involved in clinical applications that may stem from this research? and, most importantly, how do we handle the enormous database needs that will be generated by this concerted effort?

Dr. James D. Watson has accepted my invitation to head this massive undertaking for NIH as the first NIH Associate Director for Human Genome Research. A top flight group of program advisors has been selected and met for the first time in early January to begin planning for the program.

- o Data, methodology, mapping, sequencing
- o New Center for Human Genome Research
- o Coordination
  - research - data management
  - training
  - centers
- o Interagency activities
  - memo of understanding/DOE
  - Department of Agriculture - plant genome
- o International
  - Valencia
  - HUGO
  - West Germany - (ethics)
  - CIOMS/UNESCO/WHO

## THE FUTURE OF CLINICAL RESEARCH\*

By

James B. Wyngaarden, M.D.\*\*

- O Society has a vital stake in the future of clinical research for it is clinical research that will determine when, or possibly if, the continuing rich harvest of new scientific insights emerging from research will be available for improvements in the prevention or treatment of disease.
- O Clinical research offers unusual opportunities and challenges to medical students and graduate students who will be entering their productive careers or will be making career choices in the next decade.
- O Scientists entering either basic biomedical or clinical research today do so at a time of extremely rapid gains in useful knowledge. The momentum of science is both a benefit and a challenge to young men and women who would devote themselves to it.
- O "... one cannot help feel that the second half of this century will be remembered for one of the great breakthroughs of human knowledge-- perhaps the greatest to date, as it concerns the basic mechanisms of life." Christian de Duve
- O "...we are in the early stages of a genuine revolution in biological science. We're beginning to understand at a deep level how living cells and tissues really work. The effects that this revolution is now having and will have in the years ahead on medicine itself are simply incalculable." Lewis Thomas

### SOME EXAMPLES OF RECENT PROGRESS

- O Exciting new things are being learned at the frontiers of basic knowledge. Some of these findings are already being applied in patient care or diagnosis, some soon may be in general use, and others must await long-term dedicated efforts and inspired insights of young men and women such as you. Some examples:
  - o Knowledge of the intricacies of the immune system has grown dramatically in the last two decades, especially at the molecular level. The severe combined immunodeficient (SCID) mouse.

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\*Notes for Keynote Address at 1989 Eastern Student Research Forum, University of Miami School of Medicine, Miami, Florida, March 3, 1989.

\*\*Director, National Institutes of Health, Bethesda, Maryland



- o The highly sensitive polymerase chain reaction method for detection of HIV and HTLV-1 DNA and RNA. This new technique is expected to play an important part in early diagnosis of infection and the screening of blood donors as well as in efficacy testing for drugs and vaccines.
- o AIDS researchers are using two avenues of anti-retroviral drug development--the screening of large numbers of existing compounds and the designing of targeted agents that can interfere with the life cycle of the virus.
- o Scientists at NIH soon will begin using gene transfer as a means for further developing a promising new form of cancer treatment. Ultimately the scientists hope to use the gene transfer technique for cancer therapy.
- o And finally, an example of research whose applications to patient care may be longer in coming--the human genome project. Major advances have made it possible for the NIH to begin a project whose purpose is the construction of high resolution genetic and physical maps of large complex genomes. Ultimately we expect to move to the determination of the complex sequence of the DNA of any organism of interest, including man.

#### CHALLENGES OF THE NINETIES

- O To maintain the current pace of scientific advances, and particularly to press forward on such initiatives as biotechnology and the human genome project and the expansion of research on AIDS, we must ensure a continuing supply of bright and well-trained scientists. The outlook is sobering.
- O The Government-University-Industry Research Roundtable of the National Academy of Sciences projects a continuing strong demand for scientists and engineers in industry and academia but a decline in the numbers of Americans in the appropriate age groups.
- O The number of 22-year-olds at any given time is projected to drop by more than 25 percent by the year 2000. Even if the numbers were not to decline, a significant increase in the proportion of 22-year-olds who elect to pursue science and engineering degrees would be required to meet the projected research needs.
- O The Roundtable estimated that to maintain the 1985 level of potential research trainees into the 1990s the degree award rate would have to increase by 30 percent.
- O Of special significance to biomedical research is the decline in the number of baccalaureate degrees in the life sciences that has continued since 1977.

- 0 The message is clear. If we are to realize the promises implicit in the recent and rapid progress in the biosciences, we must attract greater numbers from a diminishing age segment of our population.
- 0 Dale Corson, President Emeritus of Cornell University, in a recent article on the nation's technological future wrote, "Children are being turned off to science beginning the first day of the first grade." He warned, "The problem is so deep that I think it will take generations to solve."
- 0 The challenge is daunting indeed for biomedical research, particularly when we consider the current and future needs for such categories as investigators trained for clinical research.

#### NIH AND RESEARCH TRAINING

- 0 From the time the NIH began to grow from a small laboratory and to support biomedical research nationwide, it has recognized the interdependence of training and research and the necessity for a substantial research training program.
- 0 The research training programs of NIH have been in the main an effective means for ensuring the nation's research enterprise by maintaining the flow of well-trained young scientists into research careers.
- 0 Problems arose for training programs in the late 1960s and early 1970s when it was the Administration's view that training ought to be financed by its recipient. After training and fellowship programs were summarily discontinued in 1973, the Congress passed the National Research Act authorizing the National Research Service Awards.
- 0 Since 1971, training funds administered through NIH after adjustment for inflation have declined by almost 6 percent per year, while at the same time expenditures for research have increased by 3 percent per year in real dollars.
- 0 Currently the bulk of our training support is channeled through National Research Service Awards either as institutional training grants or in the form of individual fellowships. Certain of our Institutes have special awards designed to meet particular needs--for example, the Minority Access to Research Career Awards, the Physician Scientist Award, and Awards (NRSA) for Short Term Training - Students in Health Professional Schools.
- 0 NIH has been able to maintain a relatively stable number of trainees by such measures as restricting stipends, but after four years without an increase it became essential that we adjust the stipend level. Doing so in the absence of an increase in funding for training forces a reduction in the number of trainees that can be supported.

- O A modest improvement in funding for training is requested in the FY 1990 budget that we shortly will be discussing in the annual hearings before the Appropriations committees of the Congress. The FY 1990 request includes an 8.3 percent increase for the research career and a 5.1 increase in research training programs over the FY 1989 levels. These increases do not take inflation into account, but permit the programs to be increased slightly above their current operating levels. As part of the Human Genome Initiative the research career program will be expanded by 25 awards and the research training program by 185 trainees.
- O Research training of clinicians is an especially critical matter. The need for trained clinical investigators is evident, but it is understandable that physicians-in-training have second thoughts about substantial involvement in research. They face such deterrents as:
  - o the large debt borne by recent M.D. graduates,
  - o the discrepancy between the incomes of clinical investigators and their colleagues in practice,
  - o the increasing difficulty clinical investigators experience in getting funds for their research, and
  - o uncertainties about advancement in the academic community.

In addition, one must add to this list the increasing length of time an individual must remain in training to become an effective clinical investigator. This will also add to the financial burden felt by both the trainees and their families, and may very well cause an otherwise outstanding candidate for a successful career in clinical research to enter the full-time practice of clinical medicine.

- O Institutions, as well as individuals, face economic disincentives in clinical research training programs for the changing financial structure in research-intensive medical institutions places more dependence on patient-care revenues to the detriment of clinical research.
- O Notwithstanding these evident problems, there appears to be increasing interest on the part of graduating medical students in careers of full-time research or academic activities. In the AAMC's annual survey on trends in medical students' career interest, almost a third (30.5 percent) of the class of 1988 indicated their preference for research or academic medicine. This is an increase of more than 10 percent over a similar survey of the class of 1979. On the other hand, possibly as an expression of their understanding of the difficulties, only 15.4 percent of the 1988 graduates said that they expected to be exclusively or significantly involved in research during their medical careers. This, however, is almost double the 1979 percentage of 8.7 percent. (About 10,000 students--a little over two-thirds--of the graduates respond each year.)



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## THE CLINICAL INVESTIGATOR AS AN ENDANGERED SPECIES

- O Ten years ago in my Presidential address at the Association of American Physicians I spoke on a subject that I consider to be particularly appropriate to emphasize on this occasion. The title of my address was "The Clinical Investigator as an Endangered Species."
- O Since coming to the National Institutes of Health as Director, I have become even more strongly convinced than before of the vital importance of attracting the best and brightest to careers in research--and especially of the need to interest and hold young men and women who are trained as physicians.
- O In using the term "clinical investigator" I am speaking of an individual thoroughly trained in clinical medicine and also thoroughly trained in a scientific discipline, and who, in addition, participates in both clinical and experimental endeavors as a career role.
- O The lead sentence of the cover story of the December 26, 1988 issue of MEDICAL WORLD NEWS said, "At a time of explosive innovation in biomedical science, there has been a quiet erosion in the number of physicians actively engaged in research." The article went on to note that, "Although they (physician researchers) are as successful in obtaining government grants as Ph.D. scientists, experts say fewer M.D. researchers are choosing to compete--raising concerns that some medical discoveries may never make it from the bench to the bedside."
- O NIH experience bears out the MEDICAL WORLD NEWS statement. Looking back over the past decade, the success rates of M.D. applicants for NIH competing research grants have been essentially the same as the rates of Ph.D. applicants. However, the number of new awards to both M.D.s and Ph.D.s has declined by about one-third. (SLIDE - 1)

| <u>NEW R01 AWARDS</u>       | <u>1979</u> | <u>1984</u> | <u>1988</u> |
|-----------------------------|-------------|-------------|-------------|
| Success Rates of M.D.s (%)  | 31.3        | 24.7        | 22.8        |
| Success Rates of Others (%) | 34.2        | 24.5        | 23.1        |
| Awards to M.D.s (number)    | 918         | 667         | 597         |
| Awards to Others (number)   | 2,422       | 1,756       | 1,572       |

- O Although the numbers involved are not large the proportion of postdoctoral fellowships awarded to M.D.s has remained at about 20 percent for the past 10 years. (SLIDE - 2)
- O A key measure of the entry of physicians into research is the number of NIH Young Investigator Research Awards and FIRST awards. Here again the proportions have remained fairly consistent as the numbers have increased. (SLIDE - 3)



| <u>New R23 &amp; R29 Awards</u> | <u>1979</u> | <u>1984</u> | <u>1988</u> |
|---------------------------------|-------------|-------------|-------------|
| M.D.s (number)                  | 48          | 81          | 140         |
| M.D.s (%)                       | 25.1        | 24.3        | 22.3        |
| Non-M.D.s (number)              | 143         | 252         | 487         |
| Non-M.D.s (%)                   | 72.5        | 75.7        | 77.7        |

- O The length of time devoted to postdoctoral training appears to have a substantial effect on whether the MD postdoctoral trainees apply for and are awarded grants. (SLIDE - 4), (SLIDE - 5), (SLIDE - 6)

#### WHAT TO DO ABOUT IT--CLINICAL TRIALS AS A SPECIAL CASE

- O Within biomedical research activities a new sub-enterprise--clinical trials--has developed and is undergoing rapid growth. Such studies as:
  - o The TIMI (Thrombolysis in Myocardial Infarction) Trial
  - o The Tight Control Diabetes Trial
  - o Modification of Diet in End Stage Renal Disease are of major potential significance with respect to long-term efficacy of medical care as well as its cost.
- O There is an increasing level of congressional interest in the number of clinical trials being supported through the NIH, and consequently in the training of investigators for the conduct of such trials.
- O The rapid expansion of this activity suggests that we might reexamine some of the premises on which we have developed and conducted our programs of research training. The programs have not been oriented specifically toward filling the needs for persons to carry out clinical trials. Should we structure our programs differently?
- O I have the impression that there has been a gradual change in the career course of physician investigators. My contemporaries with deep interest in research typically entered intensive postdoctoral research training after completing medical school and their specialty residency. It was from this population that the investigators who could best conduct clinical trials were drawn. But today advanced levels of expertise are required for planning and conducting the more complex trials--requirements for which even our solid postdoctoral research training did not prepare us. Further, there appears to be a trend for persons who followed the career path I mentioned to opt out of clinical care.
- O Perhaps we could provide well-trained clinical specialists with advanced training in such areas as epidemiology and biostatistics, with the thought that such training would prepare them for the sound planning and conduct of clinical trials in their specialty areas. Could such specialists be induced to take one or two years of training specific to the requirements for clinical trials?

- 804
- O Young investigators can play critical roles in a number of new, multi-institutional, centralized research efforts, and in doing so can learn skills that can later be important resources for them in academia or industry. Some of these consortium groups are parts of cancer control programs, for example, the Eastern Solid Tumor Group, the Leukemia Task Force B, and recently the AIDS Clinical trial group. In the Clinical Trial Group a continuing nationwide effort involves many institutions, drugs, and individual protocols.
  - O As we think about modifications of our training programs, we need to recognize that clinical trials in particular have created a new set of ethical issues. The problems arise in large part because of the financial consequences--some of them massive--that are bound up with the results of clinical trials. The appearance of a conflict of interest is a potential trap for every investigator involved in conducting a clinical trial. We must give more attention to the appearance and certainly to the reality of conflicts of interest as they pertain to investigators in clinical trials.
  - O The NIH had asked the Institute of Medicine to make a general assessment of our country's resources for clinical investigation. Major concerns have been raised about the future of clinical investigation in the United States because of such things as:
    - (a) fundamental changes in the organization of health care in the United States;
    - (b) major efforts at cost containment in all areas of clinical medicine;
    - (c) rapidly escalating expenses associated with drug development, and lastly;
    - (d) a reduction in the number of individuals pursuing a career in clinical investigation.
  - O The IOM study was conducted by a distinguished panel from academia and the pharmaceutical industry. Among the questions we asked the group to consider were two related to training. We asked, "How can the NIH increase interest in clinical investigation among medical students and residents?" and further, "How can the training of young clinical investigators be improved to optimize their chances of success in the peer review process?"
  - O The IOM study recommended a national training program that produces annually about 1,000 new, well-trained, clinical investigators. The committee estimated that this number would be required to replace U.S. medical school faculty members who leave their investigative careers. They recommended that each M.D. trainee should receive up to five years of experience proceeding from closely supervised training experience and moving toward increasing independence. This five-year period should include at least one year of clinical subspecialty training since it is

impossible to develop clinical investigators who lack knowledge of the particular discipline involved. The postgraduate period for the M.D./Ph.D. fellow may require a shorter period than five years (e.g., perhaps three), one of which should include clinical subspecialty training.

- O With regard to funding, the study recommends that NIH institutional clinical research training grants should be continued and be expanded to become the major funding source for the first three years of this program. In some instances, individual fellowships may be utilized to support the first three years. In most cases the final two years should be competitively funded by a mechanism similar to the NIH career development awards.
- O The IOM recommended that the training program should include, in addition to opportunities to master the fundamental biomedical science design and responsible conduct of clinical trials, a solid foundation in areas such as clinical trials methodology, biostatistics, clinical epidemiology and clinical pharmacology. In addition they recommended that efforts must be made to enhance an awareness of the ethical, social, and economic factors related to clinical investigation. This additional training program should be extended to clinical investigators in other professions as well as physicians.
- O And finally, a cautionary note for both the research enterprise as a whole and the individual scientist. It should be recognized that training programs in clinical investigation must enroll more individuals than may ultimately continue in that career. Prior to entering a rigorous training program in clinical investigation, few individuals will truly know if they have the ability, interest, and temperament to succeed as a clinical investigator. Good programs will give them the opportunity to make an honest effort to succeed in the highly competitive and, at times, extremely frustrating world of the clinical investigator. The challenge to the NIH, to academia, and to industry is to develop and nurture the kinds of training programs that will enhance our ability to translate what has been discovered in the basic sciences into medical advances that can benefit people everywhere.



STATUS AND FUTURE DIRECTIONS FOR BIOMEDICAL RESEARCH\*

BY

JAMES B. WYNGAARDEN, M.D.\*\*

OVERVIEW OF HEALTH R&D IN THE UNITED STATES

0 TOTAL HEALTH COSTS TODAY IN THE U.S. IS ESTIMATED AT ABOUT \$497 BILLION (LATEST FIGURES AVAILABLE ARE ACTUALLY ESTIMATES FOR 1987).

0 TOTAL NATIONAL HEALTH R&D IS ESTIMATED AT ONLY ABOUT 3.2% OF TOTAL HEALTH EXPENDITURES.

0 IN 1988, THE TOTAL NATIONAL SUPPORT FOR HEALTH R&D WAS AN ESTIMATED \$18.13 BILLION. OF THAT TOTAL, 35% WAS SUPPORTED BY NIH, 42% BY INDUSTRY AND 23% BY OTHER FEDERAL, STATE AND LOCAL GOVERNMENTS AND PRIVATE NON-PROFIT ORGANIZATIONS.

0 THE CROSS-OVER YEAR, WHEN INDUSTRY FOR THE FIRST TIME SURPASSED NIH IN PERCENT OF HEALTH R&D SUPPORT, WAS 1983. BUT

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\*PRESENTATION AT CHILDREN'S HOSPITAL NATIONAL MEDICAL CENTER, WASHINGTON, D.C., MARCH 11, 1989.

\*\*DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND.



WHEN WE LOOK AT ALL BASIC HEALTH RESEARCH SUPPORT WHICH TOTALLED SOME \$5.7 BILLION IN 1987, 62% WAS PROVIDED BY NIH AND ABOUT 10% BY INDUSTRY.

0 BREAKING DOWN THOSE FIGURES FURTHER, BY TYPE OF EFFORT SUPPORTED, WE FIND THESE COMPARISONS: NIH SUPPORT IN 1987 WAS ALLOCATED APPROXIMATELY 61% TO BASIC RESEARCH, 30% TO APPLIED RESEARCH AND 9% TO DEVELOPMENT. OUR INTERNAL ANALYSIS FOUND A DIFFERENT, BUT NOT SURPRISING, TREND IN INDUSTRY SUPPORT: 10% FOR BASIC RESEARCH, AND THE REMAINDER INVESTED IN APPLICATION AND DEVELOPMENT.

0 CLEARLY, GOVERNMENT AND INDUSTRY PERFORM COMPLEMENTARY ROLES IN THE ADVANCEMENT AND APPLICATION OF BIOMEDICAL KNOWLEDGE.

0 IT IS ALSO IMPORTANT TO REALIZE WHERE THIS FUNDING IS BEING SPENT: OF THE \$6.9 BILLION SPENT FOR HEALTH R&D BY INDUSTRY IN 1978, ONLY ABOUT \$273 MILLION WENT TO INSTITUTIONS OF HIGHER EDUCATION AND ONLY ABOUT \$132 MILLION WENT TO OTHER NONPROFIT ORGANIZATIONS SUCH AS HOSPITALS AND INDEPENDENT RESEARCH INSTITUTIONS. THE BULK OF INDUSTRY SUPPORT FOR HEALTH R&D, NOT SURPRISINGLY, IS SPENT WITHIN THE INDUSTRY ITSELF (\$5.4 BILLION).

0 NIH'S FUNDING IS DISTRIBUTED DIFFERENTLY, WITH THE BULK-- 63% - GOING TO INSTITUTIONS OF HIGHER EDUCATION AND ANOTHER 15% GOING

TO OTHER NONPROFIT ORGANIZATIONS, AND MUCH SMALLER AMOUNTS TO INDUSTRY AND STATE AND LOCAL GOVERNMENTS.

0 ACADEMIC RESEARCHERS GET THE MAJOR SHARE OF NIH MONEY. ABOUT 52% OF ALL NIH EXTRAMURAL MONEY GOES TO MEDICAL SCHOOLS (THIS SHARE HAS BEEN STABLE OVER THE 1980'S, VARYING NO MORE THAN A PERCENTAGE POINT OR TWO A YEAR). OTHER BIG CATEGORIES OF NIH GRANTEES ARE NONPROFIT HOSPITALS NOT ASSOCIATED WITH MEDICAL SCHOOLS, WHICH RECEIVE ABOUT 8% OF NIH MONEY, AND THE INDEPENDENT RESEARCH INSTITUTES, WHICH RECEIVE ABOUT 9%.

#### OVERVIEW OF NIH SUPPORT OVER THE YEARS

0 IT IS NOT UNCOMMON IN RECENT YEARS FOR MEMBERS OF THE SCIENTIFIC COMMUNITY TO PROCLAIM THAT "THE SKY IS FALLING", THAT THE NIH APPROPRIATION HAS BEEN SLASHED, THAT FEDERAL SUPPORT OF BIOMEDICAL RESEARCH IS CAPRICIOUS, AND THE FUTURE UNCERTAIN.

0 THIS DOES NOT DESCRIBE ACCURATELY THE CURRENT STATE OF AFFAIRS. COMMENTS OF THIS NATURE GENERATE UNNECESSARY PESSIMISM.

0 THE PAST SEVEN YEARS (82-89) HAVE SEEN A PERIOD OF SUSTAINED GROWTH FOR THE NIH, AMOUNTING TO 96% IN CURRENT DOLLARS AND 35% IN REAL TERMS. IN EACH OF THE LAST FOUR YEARS, THE NIH APPROPRIATION HAS REACHED A NEW HIGH IN CONSTANT DOLLAR TERMS.

O THE PRESIDENT'S 1990 BUDGET, WHICH I WILL DEFEND BEFORE THE HOUSE AND THE SENATE IN THE NEXT FEW MONTHS, IS \$7.5 BILLION, AN INCREASE OF 5.3% OVER THE FY 1989 BUDGET. AFTER RULING OUT THE EFFECTS OF INFLATION, THE BUDGET IS ESSENTIALLY STABLE.

o 25% AIDS

o 3.7% OTHER

O THE IMPORTANT POINT IS HOW MUCH EXCELLENT RESEARCH THAT BUDGET CAN SUPPORT. ONE WAY OF LOOKING AT THIS IS TO CONSIDER THE AWARD RATES--THAT IS, THE PERCENTAGE OF APPROVED GRANT APPLICATIONS WE ARE ABLE TO FUND. IN THE NEARLY SEVEN YEARS THAT I HAVE BEEN DIRECTOR, THE OVERALL AWARD RATES HAVE BEEN ABOUT EVEN--IN 1982, 34.7% AND IN 1988, 35.4%. IT IS TRUE BACK IN 1975, WE WERE ABLE TO FUND ABOUT 60 PERCENT OF GRANTS ELIGIBLE FOR AWARD. THE DIFFERENCE TODAY IS THE INCREASED COMPETITION FOR THE MONEY-- I.E., WE ARE RECEIVING MORE GRANT APPLICATIONS-- AND THE INCREASED COST OF THE AVERAGE GRANT.

O THUS, WE ARE HOLDING AT ABOUT 35-39%. MORE PROBLEMATIC IS THE FACT THAT SOME OF THE INSTITUTES ARE CONSIDERABLY LOWER THAN THE NIH OVERALL AVERAGE.

O NUMBER OF PROJECTS SUPPORTED OVER THE YEARS:

72-9691

73-9383

74-11,014

82-15,970

88-20,202

89-20,731

HOW SCIENCE AND THE SUPPORT OF SCIENCE HAS CHANGED OVER THE YEARS

0 COST OF THE AVERAGE RESEARCH GRANT HAS INCREASED.

0 SOME RESEARCH IS MOVING TOWARD "BIG SCIENCE". MANY YEARS AGO, SCIENCE WAS DONE BY INDIVIDUALS WORKING ALONE OR IN SMALL LABORATORIES. NOW--IN SOME AREAS OF SCIENCE--LARGER GROUPS, CROSSING INTERDISCIPLINARY LINES ARE REQUIRED.

0 THERE IS A TREND TOWARD BRINGING THE PHYSICAL AND BIOLOGICAL SCIENCES TOGETHER. FOR EXAMPLE, THE FIELD OF BIOTECHNOLOGY WILL REQUIRE SCIENTIFIC PERSONNEL TRAINED TO APPLY PHYSICS, MATHEMATICS AND CHEMISTRY TO SUCH PROBLEMS AS BIOLOGICAL STRUCTURE AT THE MOLECULAR LEVEL.

0 THE METHODOLOGY AND TECHNIQUES USED IN MODERN SCIENCE ARE INCREASINGLY SOPHISTICATED SO THAT THOSE GOING INTO RESEARCH NEED MORE AND BETTER TRAINING.

0 FOR SOME TYPES OF RESEARCH, INCREASINGLY SOPHISTICATED EQUIPMENT AND FACILITIES ARE REQUIRED. THERE IS ALSO A NEED TO



SPEND MONEY FOR KEEPING FACILITIES IN LINE WITH REQUIREMENTS FOR ANIMAL WELFARE, BIOSAFETY CONSIDERATIONS, DATA CAPABILITIES, ETC.

0 INCREASINGLY, INDUSTRY HAS ENTERED THE PICTURE, COLLABORATING WITH UNIVERSITY, HOSPITAL AND MORE RECENTLY GOVERNMENT RESEARCHERS. THIS HAS POTENTIAL FOR CHANGING DRAMATICALLY THE WAY IN WHICH SCIENCE HAS BEEN DONE IN THE PAST AND BRINGS TO THE FORE MANY CONCERNS: OPEN EXCHANGE OF IDEAS, CONFLICT OF INTEREST, SKEWING OF THE RESEARCH AGENDA, ETC.

#### NIH ABIDING PRINCIPLES FOR RESEARCH SUPPORT

0 EMPHASIS ON INVESTIGATOR-INITIATED RESEARCH. THIS IS WHERE WE TAP THE BEST AND BRIGHTEST OF THE SCIENTIFIC COMMUNITY. ALSO PLACE EMPHASIS ON BASIC DISCOVERIES.

0 RELIANCE UPON THE PEER REVIEW SYSTEM TO SUPPORT EXCELLENCE.

0 CONCERN FOR THE INFRASTRUCTURE OF ACADEMIC BIOSCIENCE-- INCLUDING, IN PARTICULAR, TRAINING THE NEXT GENERATION OF SCIENTISTS.

#### NIH RESEARCH SUPPORT RELATING TO CHILDREN

0 NEARLY ALL THE CATEGORICAL INSTITUTES--AS WELL AS THE NICHD-- SUPPORT RESEARCH DIRECTLY RELATING TO CHILDREN'S HEALTH, SO IT IS NEARLY IMPOSSIBLE TO PROVIDE A BUDGET FIGURE ON THIS.

0 SOME AREAS OF PARTICULAR INTEREST TO NICHD:

0 **VACCINE DEVELOPMENT**--PARTICULARLY AGAINST PERTUSSIS (CLINICAL TRIALS ARE PLANNED SHORTLY IN MASSACHUSETTS) AND FOR HEMOPHILUS INFLUENZA. THE LATTER IS THE LEADING CAUSE OF ACQUIRED MENTAL RETARDATION IN THE U.S. AN EARLIER VACCINE DEVELOPED BY INTRAMURAL SCIENTISTS IS EFFECTIVE IN CHILDREN ABOVE AGE 2, BUT THE PEAK INCIDENCE OF H. INFLUENZA MENINGITIS IS 5 MONTHS, AND THERE HAS BEEN NO EFFECTIVE VACCINE FOR THIS AGE GROUP.

0 **MENTAL RETARDATION**--NICHD SUPPORTS A BROAD SPECTRUM OF RESEARCH IN THIS AREA, PARTICULARLY ON DOWN SYNDROME. SCIENTISTS ARE USING THE LATEST TECHNOLOGIES TO MAP GENES OF CHROMOSOME 21; OTHERS ARE STUDYING THE BEHAVIORAL AND LANGUAGE DEVELOPMENT OF CHILDREN WITH DOWN SYNDROME TO IMPROVE THEIR INTEGRATION INTO SOCIETY.

0 **INFANT MORTALITY, WHICH IS LINKED TO LOW BIRTH WEIGHT**--THE INFANT MORTALITY RATE IN THE U.S. HAS STAYED NEARLY CONSTANT AT 7 PERCENT FOR MANY YEARS. NICHD SUPPORTS A BROAD SPECTRUM OF RESEARCH TO GET AT THE MAJOR ROOT CAUSES OF LOW BIRTH WEIGHT--

INTERGENERATIONAL AND GENETIC EFFECTS AND CERTAIN LIFE STYLE FACTORS.

0 BIRTH DEFECTS--THESE REMAIN THE NUMBER ONE CAUSE OF INFANT MORTALITY, THE RESULT OF FAULTY DEVELOPMENT. THE NICHD APPROACH IS TO SUPPORT A COMPREHENSIVE RESEARCH PROGRAM GROUNDED ON THE BASIC SCIENCES, EXPLORING EMBRYO DEVELOPMENT AND THE IDENTIFICATION AND MAPPING OF GENES RESPONSIBLE FOR EARLY DEVELOPMENT.

0 PEDIATRIC AIDS--NICHD JOINS NCI, NINDS, NHLBI, NIAID AND THE NATIONAL CENTER FOR NURSING RESEARCH. AREAS OF STUDY INCLUDE:

- THE EXTENT OF THE AIDS EPIDEMIC IN WOMEN, INFANTS, CHILDREN AND ADOLESCENTS.
- THE TRANSMISSION OF THE AIDS VIRUS FROM MOTHER TO CHILD.
- THE EFFECT OF THE VIRUS ON FETAL AND CHILD DEVELOPMENT.
- METHODS TO PREVENT THE ONSET AND PROGRESSION OF DISEASE IN HIV-INFECTED CHILDREN.
- AIDS TREATMENT.
- APPROACHES TO UNDERSTAND AND MODIFY THE BEHAVIORS AND ATTITUDES THAT CONTRIBUTE TO THE SPREAD OF AIDS.
- AND METHODS TO PREVENT THE SEXUAL TRANSMISSION OF THE DISEASE.

THE STUDIES RANGE FROM EPIDEMIOLOGICAL SURVEYS TO CLINICAL TRIALS AND BASIC RESEARCH.

0 THE NICHD HAS STARTED A MAJOR CLINICAL TRIAL TO STUDY THE EFFECTIVENESS OF INTRAVENOUS GAMMA GLOBULIN IN THE TREATMENT OF CHILDREN ILL WITH HIV INFECTION. THIS STUDY IS TESTING THE HYPOTHESIS THAT INTRAVENOUS GAMMA GLOBULIN WILL SIGNIFICANTLY REDUCE THE RATE OF THESE OPPORTUNISTIC INFECTIONS, SLOW THE PROGRESSION OF THE DISEASE, OR PREVENT OTHER PROBLEMS ASSOCIATED WITH THE DISEASE. MORE THAN 225 CHILDREN HAVE ENROLLED IN THIS STUDY, MAKING IT THE LARGEST CLINICAL TRIAL INVOLVING HIV-INFECTED CHILDREN IN THE WORLD.

0 THE NHLBI WILL SOON FUND A STUDY TO EVALUATE THE PREVALENCE AND NATURAL HISTORY OF PULMONARY AND CARDIAC COMPLICATIONS ASSOCIATED WITH HIV INFECTION IN INFANCY AND EARLY CHILDHOOD.

0 THE NINDS ALSO FUNDS STUDIES TO DETERMINE THE EFFECTS OF HIV INFECTION ON THE CENTRAL NERVOUS SYSTEM AND ON EARLY NEUROLOGICAL AND PSYCHOLOGICAL DEVELOPMENT.

0 THE NATIONAL CENTER FOR NURSING RESEARCH SUPPORTS A STUDY COMPARING THE RISK OF PERINATAL HIV TRANSMISSION IN INFANTS BORN TO MOTHERS WHO REFUSE HIV TESTING TO THAT IN INFANTS WHOSE MOTHERS ARE TESTED.



O THE NIAID NOW HAS WITHIN ITS CLINICAL TRIALS NETWORK FOURTEEN UNITS DEVOTED TO PEDIATRIC AIDS RESEARCH. THESE GROUPS ARE DOING PHASE I TRIALS OF AZT IN CHILDREN AND INFANTS AND HAS JUST COMPLETED ENROLLMENT IN A PHASE II EFFICACY TRIAL OF AZT IN CHILDREN WITH AIDS AND ARC.

O THE GENERAL CLINICAL RESEARCH CENTERS SUPPORTED BY NIH HOSTS PEDIATRIC AIDS-RELATED RESEARCH AT 12 OF ITS SITES.

O INTRAMURAL NCI SCIENTISTS WHO HAVE BEEN AT THE FOREFRONT OF TREATING CHILDREN WITH AIDS WITH CONTINUOUS INFUSION OF AZT ARE EXPANDING THEIR STUDIES TO EVALUATING A WIDE RANGE OF NEW ANTIVIRALS, IMMUNOMODULATORS, AND METHODS OF TREATING INFECTIOUS COMPLICATIONS. NCI SCIENTISTS ARE ALSO INTRODUCING AND EVALUATING ANTIRETROVIRAL THERAPY IN PREGNANT WOMEN TO TRY TO INTERRUPT THE TRANSMISSION OF HIV FROM MOTHER TO CHILD.

#### SOME COMMENTS RELATING TO CLINICAL RESEARCH

O WE ARE ENTERING A VERY EXCITING ERA FOR CLINICAL RESEARCH. THE PACE OF SCIENTIFIC DISCOVERY HAS ACCELERATED GREATLY AND THE TIME ELAPSED BETWEEN THE DEVELOPMENT OF NEW KNOWLEDGE AND ITS MEDICAL APPLICATION HAS BEGUN TO DIMINISH.

THREE EXAMPLES:

- o IN 1973, JUST 20 YEARS AFTER THE RESOLUTION OF THE STRUCTURE OF DNA BY WATSON AND CRICK, BOYER AND COHEN PERFORMED THE FIRST SUCCESSFUL RECOMBINANT DNA EXPERIMENT. IN 1978, ONLY FIVE YEARS LATER, THE FIRST RECOMBINANT HUMAN INSULIN WAS CREATED. IN 1982, HUMULIN WAS MARKETED, AND TODAY MANY OTHER RECOMBINANT PRODUCTS ARE BEING APPLIED TO TREAT HUMAN DISEASE.
  
- o IN 1973, BROWN AND GOLDSTEIN BEGAN PUBLISHING THEIR WORK ON THE CELLULAR SYNTHESIS OF CHOLESTEROL AND CELLULAR RECEPTORS FOR LOW DENSITY LIPOPROTEINS AND THEIR RELATIONSHIP TO SERUM CHOLESTEROL LEVELS AND ATHEROSCLEROSIS. THEIR FINDINGS LED NOT ONLY TO THE LIVER TRANSPLANTATION THERAPY FOR HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA, BUT ALSO TO IMPROVED AGENTS FOR REGULATING SERUM CHOLESTEROL AMONG INDIVIDUALS WITH SERIOUSLY ELEVATED CIRCULATING SERUM CHOLESTEROL INCLUDING THOSE INDIVIDUALS WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA. THE 1987 LICENSING OF THE HMG CoA REDUCTASE INHIBITOR, MEVINOLIN, FOR THE TREATMENT OF HYPERCHOLESTEROLEMIA IS A DIRECT RESULT OF THEIR WORK.
  
- o A STRIKING EXAMPLE OF THE CONTINUED REDUCTION IN THE TIME BETWEEN THE REALIZATION OF FUNDAMENTAL BIOMEDICAL

UNDERSTANDING AND THEIR DISSEMINATION INTO PRACTICE IS OFFERED BY AIDS.

- 1981-DISEASE RECOGNIZED
- 1984-CAUSATIVE VIRUS IDENTIFIED
- BLOOD TEST DEVELOPED
- IN 1986 AZT CLINICAL STUDIES INITIATED

O IF WE WANT TO CONTINUE SUCH RAPID APPLICATION, WE NEED TO MAINTAIN THE QUALITY OF CLINICAL RESEARCH IN THIS COUNTRY AND ATTEND TO A NUMBER OF CONCERNS:

O ENSURING A CONTINUING SUPPLY OF BRIGHT AND WELL-TRAINED SCIENTISTS, PARTICULARLY THOSE TRAINED IN THE COMPLEX METHODOLOGIES OF MODERN RESEARCH AND IN THE CLINICAL SCIENCES.

- O NEED TO ATTRACT MORE YOUNG PEOPLE INTO SCIENCE.
- O NEED TO ATTRACT MORE M.D.'S INTO RESEARCH CAREERS.
- O NEED TO TRAIN THESE M.D.'S TO DO INCREASINGLY SOPHISTICATED SCIENCE--NO MORE ROOM FOR THE AMATEUR.
- O PHYSICIANS-IN-TRAINING FACE DETERRENTS SUCH AS LARGE DEBT, DISCREPANCY IN INCOMES BETWEEN CLINICAL INVESTIGATORS AND PRACTICE OF MEDICINE, DIFFICULTY GETTING FUNDS FOR RESEARCH, AND THE LONG TRAINING REQUIRED.

0 WHAT TO DO ABOUT CLINICAL TRIALS AS A SPECIAL BRANCH OF CLINICAL RESEARCH.

- 0 THEY ARE BECOMING INCREASINGLY IMPORTANT (TIMI TRIAL, TIGHT CONTROL OF DIABETES TRIAL, DIET AND END-STAGE RENAL DISEASE, AIDS AGENTS), BUT THEY ARE VERY EXPENSIVE TO OPERATE.
- 0 THERE MAY BE A NEED FOR SPECIAL TRAINING FOR PEOPLE TO CONDUCT LARGE-SCALE CLINICAL TRIALS (IN EPIDEMIOLOGY/BIOSTATISTICS).
- 0 HOW TO INTEGRATE ACADEMIC/GOVERNMENT/PRIVATE NONPROFIT/INDUSTRY IN SUCH LARGE SCALE UNDERTAKINGS AND AVOIDING CONFLICT OF INTEREST SITUATIONS.

#### EXAMPLES OF ADVANCES IN BASIC SCIENCE THAT ARE APPROACHING CLINICAL APPLICATIONS

0 EXCITING NEW UNDERSTANDINGS ARE EMERGING AT THE FRONTIERS OF BASIC SCIENCE. SOME OF THESE ADVANCES ARE ALREADY BEING APPLIED IN PATIENT CARE OR DIAGNOSIS, SOME SOON MAY BE IN GENERAL USE, AND OTHERS MUST AWAIT LONG-TERM DEDICATED EFFORTS AND INSPIRED INSIGHTS OF BASIC AND CLINICAL SCIENTISTS.

SOME EXAMPLES:



0 KNOWLEDGE OF THE INTRICACIES OF THE **IMMUNE SYSTEM** HAS GROWN DRAMATICALLY IN THE LAST TWO DECADES, ESPECIALLY AT THE MOLECULAR LEVEL. **THE SCID MOUSE.**

0 **STRUCTURAL BIOLOGY.** ADVANCES IN SEVERAL FIELDS, INCLUDING X-RAY CRYSTALLOGRAPHY, NUCLEAR MAGNETIC RESONANCE, AND MOLECULAR MODELING HAVE PROVIDED A LEVEL OF KNOWLEDGE ABOUT BIOLOGICAL MATERIALS THAT MAY SOON MAKE IT POSSIBLE TO DESIGN DRUGS TARGETED AGAINST VERY SPECIFIC MACROMOLECULES OF VIRUSES. MERCK RECENTLY DEVELOPED A THREE-DIMENSIONAL STRUCTURE OF THE PROTEASE, THE ENZYME USED BY THE AIDS VIRUS TO REPLICATE ITSELF. THE HOPE IS THAT IT MAY BE POSSIBLE TO CREATE A DRUG THAT WILL INACTIVATE THE ENZYME, THEREBY JAMMING THE VIRUS'S REPRODUCTIVE MACHINERY.

0 **THE HUMAN GENOME PROJECT.**

0 SCIENTISTS AT NIH WILL SOON BEGIN USING **GENE TRANSFER** AS A MEANS FOR FURTHER DEVELOPING A PROMISING NEW FORM OF CANCER TREATMENT. THIS EXPERIMENT IS ALSO SEEN AS A POSSIBLE FORERUNNER TO CORRECTING CERTAIN GENETIC DEFECTS.

0 **AIDS RESEARCH,** OF COURSE, IS A MAJOR EMPHASIS AREA FOR NIH SUPPORT. THE AREA OF CLINICAL PEDIATRIC RESEARCH HAS LAGGED SOMEWHAT BEHIND RESEARCH IN ADULTS, BUT--AS NOTED EARLIER--IS BEGINNING TO BLOSSOM. STILL, THERE ARE MANY DIFFICULTIES IN PEDIATRIC AIDS RESEARCH. FOR EXAMPLE:

O MANY CHILDREN WITH AIDS ARE WARDS OF THE STATE AND MANY STATES DO NOT APPROVE OF SUCH CHILDREN PARTICIPATING IN EXPERIMENTAL STUDIES (NIH'S VIEW IS THAT INVESTIGATIONAL DRUGS SUCH AS AZT MAY AT THIS TIME BE THE ONLY SMALL HOPE FOR HIV INFECTED CHILDREN).

O COST OF PEDIATRIC AIDS RESEARCH IS APT TO BE HIGHER THAN RESEARCH IN ADULTS. RECRUITMENT OF CHILDREN FOR RESEARCH AS WELL AS CARING FOR PREGNANCY WOMEN, INFANTS, AND CHILDREN WHO PARTICIPATE IN RESEARCH PROTOCOLS INVOLVE A HOST OF LABOR-, PERSONNEL-, AND COST-INTENSIVE ACTIVITIES. EVEN FACTORS SUCH AS TRANSPORTATION TO THE CLINIC OR DAYCARE CAN BECOME THE CONCERN OF THE CLINICAL STAFF AND CAN SEVERELY IMPEDE THEIR ABILITY TO DO RESEARCH. THUS, WHETHER THEY ARE INFANTS OR ADOLESCENTS, HIV-INFECTED CHILDREN ARE DEMANDING OF HOSPITAL RESOURCES. SUCH PROVISION OF A WIDE ARRAY OF SERVICES (RESPIRE CARE, SOCIAL WORKERS, FAMILY COUNSELORS, DRUG ABUSE TREATMENT FOR PARENTS, ETC.) ARE CRITICAL IN ORDER TO ENSURE COMPLIANCE WITH THE PROTOCOLS AND NO LOSS TO FOLLOWUP RESEARCH.

O IN ADDITION TO THE IMPACT THAT SOCIO-ECONOMIC AND HEALTH CARE DELIVERY ISSUES HAVE ON THE RESEARCH ENVIRONMENT, REGULATORY CONTROLS ARE CLOSELY TIED WITH OUR ABILITY TO CONDUCT CLINICAL RESEARCH. TRADITIONALLY CHILDREN HAVE NOT BEEN ENTERED INTO CLINICAL TRIALS OF NEW DRUGS UNTIL THE DRUGS HAVE BEEN SHOWN TO BE SAFE AND EFFECTIVE IN ADULTS. THIS HAS ADDED CONSIDERABLY TO

THE AMOUNT OF TIME REQUIRED BEFORE INTRODUCTION OF NEW THERAPIES INTO THE PEDIATRIC POPULATION. IT IS THE NIH POSITION THAT THE LIFE-THREATENING NATURE OF HIV INFECTION MAY JUSTIFY A MODIFICATION OF THE POLICY; AND, IN CONSULTATION WITH THE FDA, TRIALS OF NEW AGENTS ARE NOW BEING PLANNED AND CONDUCTED IN SUCH A WAY THAT DEVELOPMENT AND TESTING OF THE DRUG IN CHILDREN OCCURS NEARLY IN PARALLEL WITH TESTING IN ADULTS.

O IF EXPERIMENTAL THERAPY DOES EXTEND THE LIFESPAN OF THESE HIV-INFECTED CHILDREN (AS SEEMS PROMISING WITH AZT), THEY WILL UNDOUBTEDLY HAVE DEVELOPMENTAL PROBLEMS AND NEED ADDITIONAL MEDICAL/EDUCATIONAL ATTENTION.

O ADOLESCENTS RAISE MANY SPECIAL PROBLEMS WITH REGARD TO ENROLLMENT AND TREATMENT IN CLINICAL TRIALS. THE ABILITY TO SUCCESSFULLY RECRUIT AND MAINTAIN AN ADOLESCENT ON A CLINICAL TRIAL REQUIRES SPECIAL EFFORTS BY A WELL-TRAINED CLINICAL TEAM.

O THE SPECIAL NEEDS AND UNIQUE CHARACTERISTICS OF HIV-INFECTED CHILDREN CALL FOR A REEXAMINATION, AT THE SCIENTIFIC AND REGULATORY LEVELS, OF THE METHODS TRADITIONALLY FOLLOWED IN PEDIATRIC RESEARCH. FURTHER, THE RECOGNITION OF THE SOCIO-ECONOMIC FACTORS SURROUNDING HIV-INFECTED CHILDREN WILL CONTINUE TO LEAD TO THE BROADENING OF COOPERATION AND STRENGTHENING OF LINKAGES BETWEEN THE RESEARCH COMMUNITY AND THE HEALTH CARE SYSTEM.

REMARKS\*

By

James B. Wyngaarden, M.D.\*\*

Let me begin with a warm personal welcome to His Excellency, Count Wachtmeister. I also want to welcome all of the members of the Swedish Embassy, the New Sweden Committee, and Mr. Magnus Moliteus, President of Pharmacia, Inc., who has provided us with this wonderful smorgasbord of which we are about to partake. Finally, I would like to welcome our Nobel laureates, Dr. Axelrod, Dr. Gajdusek, and Dr. Nirenberg.

Almost exactly two years ago, as part of our NIH Centennial celebration, we had a luncheon here in the Visitor Information Center. Attending were 50 of the best high school science students and their teachers from across the U.S., nominated by the Governor's office in each state. These Centennial Scholars and Teachers were joined by some 17 of the NIH Nobel laureates, including those present today. After the formalities were completed, the young students began to race from Nobelist to Nobelist getting autographs as one might see after a professional football game. The Nobelists were both astonished and charmed by this sudden outburst of youthful enthusiasm. The Centennial scholars, some of this nation's best and brightest young people, instinctively knew the deepest purpose of the Nobel Prize--to give young people, and all of us, heroes.

This May 19 I will be convening a Director's Advisory Council meeting entitled "Biomedical Research - The Next Generation of Scientists." We will be discussing a problem shared, I believe, with Sweden and most Western nations. First, we have a continuing decline in the number of young people. Second, of that smaller number, fewer young people are pursuing academic careers in science.

The implication of this decline in numbers and interest is deeply disturbing. Even now, as a whole generation of teachers and academicians are beginning to retire, the universities and research centers are finding it extremely difficult to find qualified replacements. And this is just the beginning of the trend. We know we have to improve the quality and quantity of mathematics and science teaching at all levels in our schools. We know we have to do a better job of attracting women and minority students to scientific careers. But most of all, we have to inspire youth with the adventure and excitement of scientific research. And that is part of what this "NIH Nobel Terrace" is attempting.

Some of you may have visited the NFL Pro Football Hall of Fame in Canton, Ohio, or the Basketball Hall of Fame, or even the Tennis Hall of

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\*Presented at the Opening Ceremony for the Nobel Terrace  
at the National Institutes of Health, March 17, 1989.

\*\*Director, National Institutes of Health, Bethesda, Maryland



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Fame. (I understand the Count is the number seven ranked over-60's tennis player in Sweden.) These Halls honor great athletes like His Excellency, and they inspire new generations to pursue careers in sports. The olympic gold medals inspire the same response. Well, this Nobel Terrace honors our olympians, it is our Hall of Fame.

There are many ways to present the NIH Nobel Prize statistics, but I will limit my observations to just one: NIH-supported researchers have won 15 percent of all the Nobel Prizes ever awarded. When over 90 plaques are in place, this Terrace will stand as a testimony to that accomplishment and provide the recognition that this prize truly deserves. With the added attraction of the interactive educational exhibits which are being installed on the main floor of the Visitor Information Center, we hope to siphon off some of the 23 million tourists who visit Washington each year to come see the NIH. This NIH Nobel "Hall of Fame" will inspire the young tourists to hope that they too may someday join this exalted group.

Obviously, this Nobel Terrace is just one step, but I believe it is a step in the right direction. Today's youth is desperately seeking genuine heroes. These NIH Nobelists are heroes who have pursued years of arduous research in the cause of knowledge and conquering disease.

Nobel's insatiable scientific curiosity, his humanitarianism, and his idealism are qualities that both Americans and Swedes admire. Historians can ponder how much of America's idealism is the legacy of 350 years of Swedish presence. Certainly a man like Hubert Humphrey, who ended his days here in this Clinical Center, embodied the best of humanitarian traditions from his roots in the strongly Scandinavian states of South Dakota and Minnesota. His sister, Mrs. Howard, is here with us today.

When President Franklin Roosevelt came here to Bethesda to dedicate the NIH campus in 1940, he said that the NIH mission was "to improve the health of all mankind." It was an international mandate, very much in keeping with the idealism embodied in Alfred Nobel's will that the prizes be awarded "to those who during the preceding year have conferred the greatest benefit on mankind." The proof of Roosevelt's mandate and Nobel's legacy is here on the terrace.

There are other measures of scientific excellence, but "The Prize" is the Nobel Prize. As we face this crisis in the need for young researchers, the NIH in particular, and the scientific community worldwide, owes a profound debt of gratitude to Alfred Nobel and to Sweden for "The Prize." The New Sweden '88 exhibit chronicles the life of Alfred Nobel. It is a fitting companion on the Terrace with the plaques dedicated to his heroes. Thanks to his generosity, they belong to us all.

It is now my pleasure to introduce His Excellency, Count Wilhelm Wachtmeister, Ambassador of Sweden. Count Wachtmeister presented his credentials on June 5, 1974, and he has been Dean of the Diplomatic Corps since 1986. During his years here in Washington, he and his wife, Countess Ulla, have established a circle of friends that extends far beyond the diplomatic corps, and they have been outstanding representatives for Sweden. At the end of May, His Excellency will be retiring from the diplomatic service, so let us give him a particularly warm welcome as we say at once "Farelo" and, too soon, "goodbye." Allow me to present Count Wachtmeister.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director

Mr. Chairman, it is my privilege once again to appear before you and the members of the Subcommittee to present the President's budget proposal for the National Institutes of Health. Each year we also take this occasion to tell you of research programs that we feel will be of special interest and report on our stewardship as the principal Federal agency for biomedical research. My testimony, and the presentations by the heads of the constituent units of the NIH, will provide a general outline of our current plans and present some examples of significant new insights into the biological sciences--knowledge that is being translated into better means for prevention and treatment of disease and disability. In my presentation I will refer briefly to the scientific and organizational implications of certain new programs; mention some current issues; and outline the FY 1990 budget proposal.

At the outset, however, I wish to add a special word of appreciation to you Mr. Chairman, and to the members of the Subcommittee for your interest in and support of our plan to build a Consolidated Office Building by providing for its planning and design. We are also appreciative of the funding provided for detailed design and site preparation for the Child Health/Neuroscience Facility.

By way of summary permit me to characterize the FY 1990 proposal for NIH as an expression by the Administration of its concurrence in the view, long espoused by the scientific research community that basic biomedical research should be a priority. The Administration is also committed to applied research on such priority topics as AIDS, and an area of unique scientific promise, human genome mapping. The proposal also shows recognition of the role research training plays in attracting new talent to research careers. Finally, the Administration proposes to maintain support of applied and developmental research.

In discussing our new programs, I first will mention the Human Genome Initiative. The NIH has supplied much of the impetus for the development of the knowledge and new techniques that make possible the construction of high resolution genetic and physical maps of the total genetic endowment, or genome, of any organism of interest, including man. Ultimately we expect to advance to a determination of the complex sequence of the DNA of all of the constituent genes. In addition to the enormous amounts of biomedical information and better understanding of the role of genes in human disease that will come from this effort, many important scientific and technological advances can be expected, having both basic and commercial applications.

Such fundamental genetic research is providing a better understanding of inheritable diseases ranging from juvenile myoclonic epilepsy and Tay-Sachs disease to Duchenne muscular dystrophy. From recent research a new means has been developed for diagnosing



hemophilia through direct analysis of the genome. In addition to facilitating carrier testing and prenatal diagnosis of hemophilia, this method can be used to identify genetic susceptibility to environmental agents of disease. The potential for new applications of advanced genetic research is essentially unlimited.

As we took the initial steps in developing the human genome program, it became clear that for the NIH to continue to exercise leadership in this endeavor we must establish an organizational focus to direct the project and to coordinate it within the NIH, with the National Center for Biotechnology Information of the National Library of Medicine, with other Federal and non-Federal agencies, with industry, and with various national and international scientific organizations. Accordingly, the NIH Office of Human Genome Research was created within the central administration of NIH. Dr. James D. Watson accepted my invitation to head the program as the first NIH Associate Director for Human Genome Research. Dr. Watson brings to the position the experience of his unmatched career as a scientist and scientist-administrator, and the pioneering vision that has brought him worldwide respect and recognition through the Nobel Prize and in many other ways. I am delighted that the FY 1990 budget proposes that \$100 million be devoted to the Human Genome project.

Another highlight of the FY 1990 budget proposal is the substantial increase requested for the support of research on acquired immunodeficiency syndrome. While the FY 1990 budget proposes consolidation of all funds for AIDS in the Office of the Assistant Secretary for Health, the estimate for research through the NIH is \$752.7 million, an increase of \$149 million over the FY 1989 estimate. This increase will permit research on AIDS to continue to expand in vaccine development and therapeutics, building upon such initial advances as lengthening the life expectancy of AIDS patients through the use of AZT, other drugs in combination, and improvements in the treatment of opportunistic infections.

NIH-supported researchers have developed a highly sensitive method for the detection of the AIDS-causing virus. The polymerase chain reaction technique has made it possible to identify HIV genetic sequences in infected individuals before they are positive to antibody tests. This new technique is also expected to play an important part in the screening of blood donors as well as in efficacy testing for drugs and vaccines. In the area of therapeutics the NIH is simultaneously pursuing two avenues of anti-retroviral drug development--the screening of large numbers of existing compounds and the designing of targeted agents that can interfere with the life cycle of the virus.

The plan for FY 1990 is the most comprehensive approach yet developed to bring the full resources of biomedical research to bear on the problem of AIDS. To assist in setting priorities, and to coordinate the widespread and complex activities, we have created a new unit within the Office of the NIH Director, headed by the Associate Director for AIDS Research, Dr. Anthony Fauci, who serves concurrently as Director of the National Institute of Allergy and Infectious Diseases.

The use of the gene transfer technique is another exciting development. Scientists at the NIH will soon begin using for the

first time this technique as a means for learning why a promising new form of cancer treatment seems to be effective in some patients and not in others. The experimental cancer treatment developed by Dr. Stephen Rosenberg of the National Cancer Institute makes medical use of certain cells produced in the bodies of cancer patients. These cells are capable of killing a patient's tumor cells while sparing normal cells. The tumor-fighting cells that are removed from the body, treated with a growth factor and reintroduced appear to produce remission in some patients, but not in others. In the hope of understanding why this is the case, the researchers have wanted to trace the cells after administration. The gene study is designed to label the cells for tracking in the body.

In the first experiment a bacterial gene that produces harmless but recognizable characteristics will be inserted in tumor-fighting cells from ten patients with advanced melanoma--a deadly type of skin cancer--and the altered cells will be returned to the patients from whom they were taken. Cells from a patient's blood or biopsied tissue that contain this marker can be identified easily, and from this information it is hoped that the therapy can be improved. Ultimately, the scientists hope to use the gene transfer technique for cancer therapy.

Mr. Chairman, at the time I appeared before this Committee last year, I reported that the Institute of Medicine of the National Academy of Sciences (IOM/NAS) had been asked to do an independent evaluation of various strategies to strengthen the scientific excellence of the NIH intramural laboratories. The IOM/NAS study, A Healthy NIH Intramural Program, examined the proposed alternatives and made several recommendations designed to improve the competitive position of our intramural programs with respect to recruitment and retention of senior scientists. Time does not permit me to comment on the report item by item, but I will say that in general I am gratified by the results. The study reaffirmed the importance of the intramural program, and in commenting on its high quality said there is no need for radical changes.

In this context, the Administration seeks to foster fair compensation for intramural scientists and scientists supported by NIH who work in non-profit and pharmaceutical laboratories. Appropriation language regarding extramural compensation is proposed, and additional proposals based on the Institute of Medicine Report are under study as we analyze how best to use its findings to strengthen our intramural program.

As biomedical research has become more complex and intellectually demanding, the training of researchers has become more and more a primary concern. Our training programs are not only intended to provide excellent training, they also have a critical role in attracting able young scientists into research careers. After careful consideration the NIH recommended and the Public Health Service approved an increase in the stipends for trainees to provide a level of support adequate to attract the best research trainees, even though such an increase was expected to result in a reduction of the number of trainees. For the trainees predictability is of critical importance for normally the potential researcher has only a limited time when research training can be fitted into a complex and active career. We are taking all feasible steps to ensure that the



training grants due for renewal in FY 1989 do not bear the full burden of the requisite reduction in the number of trainees. One such measure was to maintain tuition payments for FY 1989 at the FY 1988 level, and another possibility is to request a reprogramming of funds.

Mr. Chairman, the overall FY 1990 budget request for the National Institutes of Health is \$6,776.7 million, an increase of \$233.3 million or 3.6 percent over the comparable FY 1989 budget. The request places additional emphasis on basic biomedical research, providing an increase of 6.6 percent in this category of activity. For the first time the budget includes a separate request for the new National Institute on Deafness and Other Communication Disorders.

In the FY 1990 request all funding for AIDS is consolidated in a special account in the Office of the Assistant Secretary for Health. Consequently, in the following discussion of the FY 1990 budget for NIH, and in comparisons with FY 1989, the estimates for AIDS will be excluded.

Investigator-initiated research continues to be accorded the highest priority in the NIH budget. The FY 1990 request will support a total of 19,773 research grants as compared to 20,130 in the current fiscal year. The support for research project grants would be increased by 5.7 percent over the current year and would total \$4,034.5 million.

The request will support 4,556 competing research project grants. This is a decrease of 572 competing awards from the number to be made this year. The number results from our effort to achieve a balance between levels of downward negotiation required and the number of grants to be supported. The awards include as many as 100 research grants that are planned to be funded from the Director's Discretionary Fund, an amount of \$25 million requested for FY 1990 that can be allocated to the individual NIH components and will allow the NIH to be more responsive to emerging research opportunities and health priorities.

The NIH request for research centers of \$551.7 million would support 572 centers. Due to the high priority attached to General Clinical Research Centers, as well as the higher costs associated with clinical research, these awards will receive an aggregate increase of 3.4 percent. The total allocated to all other research center awards will be reduced slightly from the FY 1989 level.

The FY 1990 request includes an 8.3 percent increase for the research career development programs and a 5.1 percent increase in research training programs.

In recognition of the importance of programs for minorities and small colleges, a 3.4 percent increase has been provided for the Minority Biomedical Research Support Program, the Minority Access to Research Careers Programs, the Research Centers in Minority Institutions Program, and the Academic Research Enhancement Award Program.

The excellence of NIH scientists and the intramural facilities, including the Warren Grant Magnuson Clinical Center, afford many unique research opportunities. The FY 1990 request for \$733.9

371  
million provides an increase for intramural research of 6 percent over the FY 1989 level. This increase will be used to cover the costs of administrative increases and with improved efficiency in procurement practices will offset the effects of inflation on the costs of basic laboratory and hospital supplies and equipment.

Thank you. I would be pleased to respond to any questions you may have.



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For Release Upon Delivery

STATEMENT BY

JAMES B. WYNGAARDEN, M.D.

DIRECTOR

NATIONAL INSTITUTES OF HEALTH

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

HOUSE COMMITTEE ON POST OFFICE AND CIVIL SERVICE

APRIL 27, 1989



Mr. Chairman and Members of the Committee:

I appreciate the opportunity to address the Committee and present my views on the report of the National Commission on the Public Service. I will focus on those recommendations relating to recruitment and retention of senior career officials, and will discuss the impact these problems are having on this Nation's Federal biomedical research programs.

The Commission sounded an alarm that the uncompetitive salaries of members of the Senior Executive Service are undermining the Government's vital science programs. Their report warns that the failure to increase these salaries will substantially diminish our ability to recruit and retain the highest quality biomedical researchers, engineers and other senior career executives who manage essential services in the Government. The report suggests that the urgency of raises for career Senior Executives may be even more critical than at the political level. The Commission recommends "prompt action by the President and Congress to raise the cap on the Senior Executive Service, even if this means that their pay in some instances could exceed that being received by the political appointees above them." Let me now address how inadequate salaries for senior career officials is affecting our Nation's biomedical research efforts.

The National Institutes of Health is an agency of the Department of Health and Human Services. It is the Federal focal point for health research. Our mission is to discover new knowledge that will lead to better health for everyone. NIH works toward this mission by: conducting research in

our laboratories; supporting the biomedical research of non-Federal scientists in universities, medical schools, hospitals, and research institutions throughout the country and abroad; assisting in the training of research investigators; and fostering and supporting the dissemination of biomedical and health information to scientists, physicians and other health professionals and to the public.

NIH has become the world's premier biomedical research institution because of the outstanding quality of its senior staff, who have made significant contributions to the major advances in the biomedical sciences, leading to improved methods for diagnosis, treatment and prevention of many human diseases. NIH research is the leading contributor to the new biotechnology. Within the last two decades, many of these advances have opened potentially valuable and lucrative commercial applications and have caused a dramatic increase in the competition for top caliber senior researchers and science managers in the private and academic sectors. Federal compensation for these employees has not kept pace with the increased competition. As a result, NIH has been experiencing problems recruiting and retaining senior level personnel of the prominence and stature required to lead and conduct national research programs into the causes and treatment of major human afflictions.

There are currently 174 highly qualified and talented members of the Senior Executive Service at NIH. Of these, 52 are physicians, and 103 have Ph.D. or other doctorates. Virtually all of these individuals can command substantially higher salaries in the private or academic sectors,

and many have standing employment offers. All have been experiencing severe limitations in their salaries over the last several years and the lack of a pay raise has affected their morale.

Our studies show that on the average, NIH Senior Executive Service physicians are paid about one-half as much as their academic counterparts. Other NIH doctoral staff who belong to the Senior Executive Service are paid 19 percent less than comparable positions in research-intensive universities. Furthermore, the gap in compensation between the NIH and American medical schools is increasing. When I came to NIH in 1982, our medical officers who were in the SES were paid \$39,000 less than their counterparts in American medical schools. Today that gap has widened to \$99,000. Many of our senior scientists are considering whether to remain with NIH because of these salary disparities.

Our situation can best be illustrated by the results obtained from an informal survey NIH recently conducted of employment offers that have been made to our permanent scientific staff within the last two years. Of the senior physicians who responded to the survey, 83 percent reported receiving one or more offers ranging from \$100,000 to \$500,000. The average employment offer was \$166,000, approximately twice what they are making at NIH. Among senior non-physician doctoral staff responding, 54 percent received employment offers of at least \$10,000 more than their NIH salary. The average offer was \$105,000, which is 50 percent higher than they are now earning. With offers of this magnitude, NIH can expect to

lose a substantial number of key senior scientists and science administrators.

The compensation gap has also made recruitment exceptionally difficult. For example, since 1980 NIH has not been able to recruit a single research scientist into the Senior Executive Service from the private or academic sectors to engage in the independent conduct of a clinical or basic biomedical research program. In 1980, NIH had 108 Intramural researchers in the SES. Since then, we have had 59 vacancies, and have been able to fill only 29, all from within the Government. In addition, there are numerous cases of top candidates expressing substantial interest in senior positions at NIH who withdrew from consideration because we could not offer an adequate salary or benefits. Among these, a large number of prominent candidates for five different Institute Director positions declined further consideration because NIH could not match their current salaries and benefits. During this same period of time, over twenty prestigious senior scientists expressed interest in positions for which NIH was recruiting. All declined further consideration because they were currently earning salaries ranging from 20 to 263 percent more than NIH could pay.

During the last year, NIH has also attempted to recruit such senior staff as a pharmacologist to conduct AIDS-related drug analysis studies; a scientist to undertake research in nerve regeneration; a cancer radiation therapist; and several physicians in a variety of much needed surgical specialties, including general cancer, thoracic and neurosurgery. NIH was



not successful in filling any of these positions owing to inadequate compensation. As a result, a number of promising basic and clinical research initiatives have not been pursued, and several other existing programs were curtailed.

Salary differentials with the private sector also affect our ability to retain senior staff. While many of them remain at NIH because of its fundamental mission and its unparalleled reputation for scientific excellence, recruiters from academia and industry make highly attractive offers to our senior staff that only too often are accepted.

In the last ten years, NIH has suffered a net loss of 28 percent of its research scientists in the Senior Executive Service. All left NIH to accept positions in academic institutions, industry, and independent research laboratories at salary increases ranging from 50 to 300 percent. In the last six years, NIH has lost a Deputy Director and five Institute Directors because of salary considerations. Recently, a number of prominent scientists have left NIH for salary reasons. These losses include one of the country's foremost experts in breast cancer, and the individual responsible for setting up a national network of cooperative clinical groups who conduct trials for testing and understanding new treatments for cancer on a national basis.

A recent independent study of the NIH intramural research programs conducted by the Institute of Medicine of the National Academy of Sciences confirms our findings. In this report, the Institute of Medicine states,

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"The reduction in the number of senior researchers, the increasing age of those remaining, the failure to successfully recruit from outside, and the evidence of generally noncompetitive salaries justifies NIH concerns about their future ability to recruit and retain senior researchers and research administrators. This is particularly serious since many of the current researchers are approaching retirement age."

One of the Institute's recommendations was that "Congress authorize NIH to develop and implement a personnel demonstration project tailored to overcome the deficiencies of the current system." The IOM suggested that the plan feature simplified hiring, classification, and pay administration, similar to the demonstration now being conducted by the National Institute of Standards and Technology. The Institute also recommended an occupation-specific pay standard, based on surveys of market comparability; the ability to exceed Federal pay caps; portable retirement systems to encourage non-Federal scientists to join NIH; and employment ceilings set by budget, rather than personnel ceilings.

The Department of Health and Human Services has developed a proposal, called the Senior Biomedical Research Service (SBRS), that is responsive to the IOM recommendations, and would help overcome recruitment and retention problems affecting senior scientists. The SBRS is an entirely new personnel system in the excepted service and would provide provisions for salaries based on market comparability, a portable retirement system, and other flexibilities which we find are necessary to better manage and

motivate our scientific workforce. We are currently working with the Office of the Secretary to revise and update this proposal.

Equally important is the effect that the lack of a pay raise for senior scientists has had on our junior and mid-level scientists. NIH is relatively successful in recruiting and developing bright and promising post-doctoral research scientists. Our employment trends indicate that as these scientists progress and begin to encounter salary compression due to pay limitations in the senior ranks, they leave the Government just as they are entering the peak of their careers. NIH encourages this to some degree because it fosters cross-fertilization of ideas between NIH and the academic community, and allows NIH to bring in a new cadre of young bright people with fresh ideas. However, we expect that a continued limitation on the pay of senior level staff may accelerate these departures. If this occurs, NIH will have fewer well trained researchers available for advancement to senior leadership positions.

NIH offers advantages that for many researchers have offset the salary differentials. These include the intellectual stimulation and prestige of being a part of NIH, scientific freedom to choose their own research pursuits, access to state-of-the-art equipment, freedom from administrative and teaching responsibilities, opportunities for rewarding associations with outstanding scientists within many disciplines, and opportunities for consulting, although these are subject to restrictions. In the face of the widening salary gap, these advantages become less compelling.

Our recruitment and retention difficulties are occurring at a time of great challenge and opportunity in the biomedical sciences. If NIH is to meet this challenge, it is vital that we have a core of first-class senior researchers and science managers who will provide the necessary innovation and leadership. To do so, NIH must have the capacity to compete nationwide for the best available scientific talent. I firmly believe that an increase in compensation is one of the essential first steps toward restoring NIH to a fully competitive posture and demonstrating the commitment of the Federal Government to the retention of these valuable and highly qualified senior scientists.

Mr. Chairman, this concludes my prepared statement. I would be pleased to answer any questions that you or other members of the Committee may have.





## National Institutes of Health

## Statement of the Director

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Mr. Chairman, it is my privilege to appear before you and the members of the Subcommittee to present the President's budget proposal for the National Institutes of Health. I will also take this occasion to tell you of research programs that we feel will be of special interest and to report on our stewardship as the principal Federal agency for biomedical research. My testimony, and the presentations by the heads of the constituent units of the NIH, will provide a general outline of our current plans and present some examples of significant new insights into the biological sciences--knowledge that is being translated into better means for prevention and treatment of disease and disability. In my presentation I will refer briefly to the scientific and organizational implications of certain new programs; mention some current issues; and outline the FY 1990 budget proposal.

Before presenting my formal statement, I wish to express congratulations to you Mr. Chairman upon your assumption of the leadership of this important Subcommittee, and thank you for the interest you have already shown in the NIH by your visits to the campus. We are immensely pleased to have you and the other members of the committee come to Bethesda to learn first-hand about our people and our activities.

By way of summary permit me to characterize the FY 1990 proposal for NIH as an expression by the Administration of its concurrence in the view, long espoused by the scientific research community that basic biomedical research should be a priority. The Administration is also committed to applied research on such priority topics as AIDS, and an area of unique scientific promise, human genome mapping. The proposal also shows recognition of the role research training plays in attracting new talent to research careers. Finally, the Administration proposes to maintain support of applied and developmental research.

In discussing our new programs, I first will mention the Human Genome Initiative. The NIH has supplied much of the impetus for the development of the knowledge and new techniques that make possible the construction of high resolution genetic and physical maps of the total genetic endowment, or genome, of any organism of interest, including man. Ultimately we expect to advance to a determination of the complex sequence of the DNA of all of the constituent genes. In addition to the enormous amounts of biomedical information and better understanding of the role of genes in human disease that will come from this effort, many important scientific and technological advances can be expected, having both basic and commercial applications.

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hemophilia through direct analysis of the genome. In addition to facilitating carrier testing and prenatal diagnosis of hemophilia, this method can be used to identify genetic susceptibility to environmental agents of disease. The potential for new applications of advanced genetic research is essentially unlimited.

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form of cancer treatment seems to be effective in some patients and not in others. The experimental cancer treatment developed by Dr. Stephen Rosenberg of the National Cancer Institute makes medical use of certain cells produced in the bodies of cancer patients. These cells are capable of killing a patient's tumor cells while sparing normal cells. The tumor-fighting cells that are removed from the body, treated with a growth factor and reintroduced, appear to produce remission in some patients, but not in others. In the hope of understanding why this is the case, the researchers have wanted to trace the cells after administration. The gene study is designed to label the cells for tracking in the body.

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As biomedical research has become more complex and intellectually demanding, the training of researchers has become more and more a primary concern. As an example of expanded need, growth in the field of biotechnology will depend upon adequately trained scientific and technical personnel who have been trained to apply physics, mathematics, and chemistry to such problems as biological structures at the molecular level. Special interdisciplinary training programs have been developed to meet the new needs of biotechnology. Mr. Chairman, your immediate predecessor was deeply interested in this subject, and encouraged us to develop the postdoctoral and senior fellowships in biotechnology. Certain of these have been named in his honor, and shortly we will be announcing the first Lawton Chiles Fellowships.



While all of our training programs are directed to provide necessary training, they also play a critical role in attracting able young scientists into research careers. After careful consideration the NIH recommended and the Public Health Service approved an increase in the stipends for trainees to provide a level of support adequate to attract the best research trainees, even though such an increase was expected to result in a reduction of the number of trainees. For the trainees predictability is of critical importance for normally the potential researcher has only a limited time when research training can be fitted into a complex and active career. We are taking all feasible steps to ensure that the training grants due for renewal in FY 1989 do not bear the full burden of the requisite reduction in the number of trainees. One such measure was to maintain tuition payments for FY 1989 at the FY 1988 level, and another possibility is to request a reprogramming of funds.

Mr. Chairman, the overall FY 1990 budget request for the National Institutes of Health is \$6,776.7 million, an increase of \$233.3 million or 3.5 percent over the comparable FY 1989 budget. The request places additional emphasis on basic biomedical research, providing an increase of 6.6 percent in this category of activity. For the first time the budget includes a separate request for the new National Institute on Deafness and Other Communication Disorders.

In the FY 1990 request all funding for AIDS is consolidated in a special account in the Office of the Assistant Secretary for Health. Consequently, in the following discussion of the FY 1990 budget for NIH, and in comparisons with FY 1989, the estimates for AIDS will be excluded.

Investigator-initiated research continues to be accorded the highest priority in the NIH budget. The FY 1990 request will support a total of 19,773 research grants as compared to 20,130 in the current fiscal year. The support for research project grants would be increased by 5.7 percent over the current year and would total \$4,034.5 million.

The request will support 4,556 competing research project grants. This is a decrease of 572 competing awards from the number to be made this year. The number results from our effort to achieve a balance between levels of downward negotiation required and the number of grants to be supported. The awards include as many as 100 research grants that are planned to be funded from the Director's Discretionary Fund, an amount of \$25 million requested for FY 1990 that can be allocated to the individual NIH components and will allow the NIH to be more responsive to emerging research opportunities and health priorities.

The NIH request for research centers of \$551.7 million would support 572 centers. Due to the high priority attached to General Clinical Research Centers, as well as the higher costs associated with clinical research, these awards will receive an aggregate increase of 3.4 percent. The total allocated to all other research center awards will be reduced slightly from the FY 1989 level.

The FY 1990 request includes an 8.3 percent increase for the research career development programs and a 5.1 percent increase in research training programs.

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In recognition of the importance of programs for minorities and small colleges, a 3.4 percent increase has been provided for the Minority Biomedical Research Support Program, the Minority Access to Research Careers Programs, the Research Centers in Minority Institutions Program, and the Academic Research Enhancement Award Program.

The excellence of NIH scientists and the intramural facilities, including the Warren Grant Magnuson Clinical Center, afford many unique research opportunities. The FY 1990 request for \$733.9 million provides an increase for intramural research of 6 percent over the FY 1989 level. This increase will be used to cover the costs of administrative increases, and with improved efficiency in procurement practices will offset the effects of inflation on the costs of basic laboratory and hospital supplies and equipment.

Thank you. I would be pleased to respond to any questions you may have.



For Release on Delivery

STATEMENT

BY

JAMES B. WYNGAARDEN, M.D.

DIRECTOR

NATIONAL INSTITUTES OF HEALTH

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

MAY 4, 1989



Mr. Chairman and members of the subcommittee: I am Dr. James Wyngaarden, Director of the National Institutes of Health. I have been asked to discuss the investigation by the National Institutes of Health into issues raised in connection with the publication in the journal Cell of an article entitled, "Altered Repertoire of Endogenous Immunoglobulin Gene Expression in Transgenic Mice Containing a Rearranged Mu Heavy Chain Gene." The article was co-authored by David Weaver, Moema H. Reis, Christopher Albanese, Frank Costantini, David Baltimore, and Thereza Imanishi-Kari. We had considered this case to be closed on January 31 of this year but, as we have advised you, new questions have prompted us to reopen our investigation.

Following the issuance of our report on this case, Dr. Margot O'Toole, who first challenged the findings in the Cell paper, continued to express concerns and raise questions. In particular, she requested a copy of all the data for Figure 1. During the course of our effort to fulfill this request, Dr. Thereza Imanishi-Kari told a member of my staff that the data for some of the points in the Figure were not recorded in a laboratory notebook; that these measurements were made a day or so after the others; and that they were recorded directly on the Figure. Dr. Imanishi-Kari went on to say that she had reorganized some of her laboratory notebooks. We interpret her statement to mean that this occurred in preparation for the various inquiries into the Cell paper and, at least in some instances, at times well after the experiments were actually conducted. These revelations of unorthodox data handling practices have prompted us to initiate a detailed audit of all the

data upon which all the figures, tables, and text of the paper in question are based.

As you know, immediately after we advised you of our reopening of the investigation, Subcommittee staff briefed us on the results of a forensic examination of the laboratory notebooks, which raised additional questions about the data. We are indebted to both Dr. O'Toole and the staff of this Subcommittee for their interest and perseverance in seeking a complete resolution of this case. We look forward to their continuing cooperation as we pursue our investigation. In connection with our reopening of the investigation, we have contacted the Office of the Inspector General of the Department of Health and Human Services to determine what assistance they might offer us in analyzing the forensic evidence and in conducting our further investigation.

Late last year, while my senior staff and I were reviewing the findings and recommendations of our expert panel, Dr. O'Toole raised the possibility that apparently original laboratory data had been fabricated at a later time. We investigated this possibility but considered it unlikely on the basis of written assurances from all the members of the Wortis Committee at Tufts that, during their review in 1986, they had seen the particular data that Dr. O'Toole questioned. If the Wortis Committee had been unable to provide us this assurance, our plan was to proceed with a forensic analysis of the original data, which at that time were in the Subcommittee's possession.

The new information that you have shared with us on this case is extremely disturbing. During our reopened investigation, we shall reassess everything that we know about this case in determining whether misconduct is involved.

We have learned a lot about the problems that must be faced in investigating cases as complex and technically advanced as this one. It clearly is important to distinguish between scientific error and misconduct, but such distinctions frequently are very difficult to make in practice. We must recognize that allegations of error may lead us to findings of falsification or misrepresentation, and we must also ensure that the procedures in place at both awardee institutions and the NIH do not require too high a threshold before a formal investigation is begun. On the other hand, we must not view every disagreement among scientists as a charge of misconduct which must be investigated. Scientific experiments often yield results with multiple interpretations.

Errors or misinterpretations of data sometimes occur during the normal course of scientific discovery; these mistakes frequently are discovered as scientists attempt to replicate the work of others, as a prerequisite for moving on to the next step of scientific knowledge. At the cutting edge of any aspect of science, hypotheses and the experiments to test them often burst forth in a surge of creativity and enthusiasm. Under these circumstances, it is paradigmatic that false leads may develop and some errors will be made.

Because of the complexities of modern science and the difficulty on occasion in distinguishing between misconduct and error, it is clear to us that the



investigation of cases involving complex issues must be performed principally by scientists and by science-based agencies, and not be directed by individuals who are unfamiliar with the relevant scientific subject matter or how scientific research is done.

In this particular case, possible scientific error was alleged but, prior to and during the investigation, there was no clear allegation of scientific misconduct. For that reason, neither of the institutions involved initiated a formal investigation. NIH did conduct a formal investigation through a panel of scientists with expertise in the field addressed in the paper. I would like to thank the experts who comprised our scientific investigative panel. They are senior scientists who have made major contributions to the advancement of our knowledge in immunology and immunogenetics. They diverted considerable time, energy, and intellect from their own research projects in order to carry out their charge.

The scientific panel was asked to: (1) determine whether the published article in question was scientifically accurate, based on the original data; (2) if inaccuracies were found, to describe their nature and extent, including a statement as to whether misrepresentation or other misconduct was involved; and (3) recommend appropriate corrections to the scientific literature if inaccuracies were found. They did consider the possibility that misconduct might be involved in the case they were investigating. Based on the data that were available to them at the time, they found some factual inaccuracies and had serious concerns about the sensitivity and specificity of certain reagents used in generating data for the article, however, they concluded that most of



these problems represented "inadvertent errors of understanding and communication" among the three principal authors. Their examination of the raw laboratory data and their interviews revealed "no evidence of fraud, misconduct, manipulation of data, or serious conceptual errors." In light of the subsequent questions about the data, our task, difficult as it may be, is to be more alert to those situations in which a forensic examination may be needed. For this reason, in the future when there are questions about data authenticity or availability, we plan to have an individual with forensic experience work with each panel of scientists NIH appoints.

Another area of considerable concern to us, as we know it is to you, is the fate of the whistleblower in such undertakings. These persons clearly are very important in identifying instances that must be investigated. At present, we have only limited authority to protect those who, in good faith, raise allegations of scientific error or misconduct. We are sympathetic toward efforts that would provide appropriate protection to whistleblowers. Clearly, Dr. O'Toole has taken considerable risk in bringing this case to the attention of officials at MIT and Tufts University and insisting that the truth be learned. We are concerned that Dr. O'Toole's scientific career has been damaged, simply because she has pursued her convictions. We believe these kinds of risk can be ameliorated only if the scientific community is firm in its goals to maintain and promote high ethical standards, to allow and to support individuals' rights to speak out when they believe wrong has been committed, and to look forthrightly and objectively to determine the truth.

Mr. Chairman, progress in science is almost wholly dependent on scientists who, working alone or in groups, develop hypotheses, design and perform experiments, to test those hypotheses, and then communicate their results and conclusions to others, who use those findings as a basis on which to build their own hypotheses and experiments. Thus, the whole scientific enterprise, and the advancement of our biomedical knowledge, depend heavily on the trust that scientists can place on each other and the confidence that the general public can place on the work of scientists.

Deliberate attempts on the part of a small minority of scientists to deceive others about scientific procedures followed, or scientific results attained, undermine this foundation of trust. Perhaps because of the very need for scientists to be able to trust each other and to build on the work of others, it has been difficult for much of the scientific community to accept the fact that incidents of scientific misconduct do occur, are a serious problem, and must be dealt with firmly. It is of the utmost importance to all of us to preserve the reputation for integrity that science has earned over the centuries.

We believe that both NIH and the scientific community are more clearly focused on the topic of misconduct in science than they have been at any time in the past. This concern, coupled with experience and knowledge gained from this and other investigations of possible scientific misconduct, will lead to improvements in our procedures.

Regulations are being put in place to address further the problem of scientific misconduct and its prevention. A final rule addressing "Responsibilities of Applicant Institutions for Dealing with and Reporting Possible Misconduct in Science" was approved by the Secretary of the Department of Health and Human Services and submitted to the Office of Management and Budget (OMB) on April 4; it currently is under OMB review. As required by the Public Health Service Act, this final rule would implement an assurance system, under which all institutions applying for or receiving funds for biomedical or behavioral research under the Public Health Service Act must have written policies and procedures for dealing with misconduct in science. In addition, the compliance section of the draft final rule states the Public Health Service's expectation that institutions will foster a research environment which discourages misconduct in all research and which deals forthrightly with allegations of misconduct.

I have recently established the Office of Scientific Integrity in my immediate office to deal with oversight and investigations into allegations of scientific misconduct. This office currently is being staffed and already is functional. It will serve all the Public Health Service agencies. Also being established within the Office of the Assistant Secretary of Health is the Office of Scientific Integrity Review, which will provide oversight for investigations performed by the Office of Scientific Integrity and will recommend appropriate sanctions. The formation of this second office will enable the Director and other senior NIH staff to be more intimately directly involved in investigations than heretofore has been possible for me. In the past because of my role as final decisionmaker, I have not been involved in

the details of specific investigations but only have been briefed in general terms regarding their progress.

We have attempted to be responsive to the issues which the Congress, as well as individuals and other organizations, have brought to our attention. We anticipate that the measures which we already have taken will lead to increased emphasis on the fundamental imperative of ethical behavior in science, as well as to better investigations of allegations of scientific misconduct. However, we also know that there still is much to be learned in the development of the best policies and procedures in this area. The NIH is working with the Office of the Assistant Secretary for Health and other PHS research agencies to review and, as needed, develop new policies and procedures for investigating and preventing misconduct in biomedical and behavioral research.

I would be pleased to answer questions that you may have.





REMARKS\*

by

James B. Wyngaarden, M.D.\*\*

"Building 31," as the edifice behind me was previously known, and Senator Pepper share a date in common. Building 31 was first dedicated in 1962. It was the year that Claude Pepper returned to Washington as a Congressman from Florida. In his autobiography, "Pepper--Eyewitness to a Century," he recalls that year --

"The first time I was addressed as 'Congressman' (by Senator-elect Edward Kennedy, by the way) I was startled. For the fourteen years I was in the Senate and for the dozen years after when I practiced law, almost everyone called me 'Senator.' Almost everyone . . . still does."

Besides hearkening back to a time when Senator Kennedy was a Senator-elect, 1962 was an important year for Senator Pepper. True to his form, at the age of 62, when many of us would be contemplating retirement, he had sought and won elected office.

Claude Pepper was born September 8, 1900, on a farm near Dudleyville, Alabama. He has truly been an eyewitness to the Twentieth Century. In his autobiography he mentions meeting Orville Wright and greeting the crew of the Apollo spaceship. He appeared twice on the cover of Time magazine--in 1938 as a young champion of President Franklin Roosevelt's New Deal and in 1983 as a champion of Social Security and a better deal for the elderly. He was a confidante of FDR and met with Churchill, Stalin, DeGaulle, and other key players on the world stage. Every President since FDR has sought his counsel and advice. The plaque which is at the entrance of the Pepper Building is directly above the 1960 cornerstone with Dwight D. Eisenhower's name on it. In 1948, Senator Pepper attempted to convince Eisenhower to run for President as a Democrat. Now Senator Pepper's name "balances the ticket" with his friend Ike.

Most of us know Senator Pepper for his ardent advocacy for the elderly and his recent efforts in creating the Deafness Institute, but he has accomplished much, much more for NIH and the nation.

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\*On the occasion of the dedication of the Claude Denson Pepper Building at NIH, on May 10, 1989.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

Senator Pepper grew up in the rural deep South of Alabama and Texas. Always gifted with words, his first job was teaching high school at 17. He worked in steel mills and other jobs, completing his undergraduate degree at the University of Alabama in 1921. After a brief stint in the Army, he went to Harvard Law School on a post-World War I equivalent of the G.I. bill, earning his law degree in 1924. He taught law at the University of Arkansas for a year, and then moved to Florida where he began his law practice and launched his political career.

In 1929 he won election to the Florida state legislature. His first bill exempted the elderly from having to pay for fishing licenses, setting a theme for a lifetime. In 1931 he was defeated for re-election because he refused to support a bill censuring Mrs. Herbert Hoover for inviting the wife of a newly elected black congressman to tea at the White House. I think it is most appropriate that the Pepper Building houses the NIH Equal Employment Opportunity office.

In December of 1936 he married Mildred Webster, who was the light of his life until her death in 1979. In January of 1937 he was sworn in as the junior Senator from the state of Florida and appointed to the Senate Committee on Labor and Public Welfare. One of his first official acts was to sponsor the legislation which established the National Cancer Institute, once again setting a theme for a lifetime.

He visited Europe on the eve of World War II, and saw the real menace of Nazi Germany. He initiated the first Lend Lease bill to support the Allies while most of his colleagues remained unengaged.

Senator Pepper's interest in health matters increased and in 1944 he chaired the Subcommittee on Wartime Health and Education. He was disturbed that the Selective Service had found one-third of the men examined for induction to be either physically or mentally unfit for duty. Senator Pepper was also aware of the enormous progress made by the well-funded wartime research efforts in penicillin production, malaria drugs, plasma and vaccine development. In these hearings a clearer picture of the relationship of the value of research to American's health emerged, and set the agenda for the postwar development of the nation's biomedical research programs. At the conclusion of these hearings Senator Pepper stated that "The volume of research which is carried out in the medical field, should, in my opinion, not be limited by lack of money."

His opinion was shared by his friend and supporter, Mrs. Mary Lasker, who helped him select witnesses for his Subcommittee hearings. Together with their mutual friend, Mrs. Florence Mahoney, they set out to change the scope of American's biomedical research enterprise. By 1948, they had settled on the then National Institute of Health as the focal point for their intense efforts. Senator Pepper sponsored a bill



that year which established the National Heart Institute and changed our name to the National Institutes of Health. In short, he christened us and went on to sponsor legislation that created the first five of the then six NIH Institutes. In fact, ultimately, all but one NIH Institute was sponsored by Senator Pepper. He is the legislative father of the modern NIH.

A key facet of Senator Pepper's NIH Institute concept was an extramural granting authority, changing NIH from a small intramural program to a national force. The National Cancer Institute began with \$140,000 specifically identified as grant funds. The total NIH budget in 1938 was \$464,000 and we had 912 employees. By 1950, the year Senator Pepper left the Senate, the NIH budget was \$59 million with \$43 million in grants, and we had 2,888 employees. Much of this phenomenal growth was due to Senator Pepper's and Mary Lasker's combined efforts and their deep faith in the biomedical research enterprise.

His subsequent unstinting efforts on behalf of Social Security, Medicare, Medicaid, the mentally ill, the elderly, the hearing impaired, and other health concerns are well known. Senator Pepper recently introduced legislation establishing a National Center for Biotechnology Information at the National Library of Medicine for organizing and disseminating the information gained in the human genome research program. This was a visionary bill; one that will impact medicine far beyond the 20th century. Senator Pepper is an "eyewitness" to this century, but his vision extends much further.

So it is completely appropriate that the home of the 13 NIH Institutes, the meeting place of their advisory councils, and the center of their extramural grant operations be called the Claude Denson Pepper Building. In 1937 he started the engine of the modern NIH, in 1948 he set the vehicle in motion, so that even in 1962 "Building 31" was already the Pepper Building. The Claude Denson Pepper Building stands as a lasting monument to his vision and dedication to biomedical research and the nation's health. Please join me in a round of applause for Senator Pepper to express our gratitude.

Thank you.

Now, I would like to ask Senator Kennedy to join me in unveiling the sign.





## STRATEGIC PLANNING FOR BIOMEDICAL RESEARCH\*

BY

JAMES B. WYNGAARDEN, M.D.\*\*

In addressing the subject of "Strategic Planning for Biomedical Research", the dissonance between the words "research" and "planning" is resolved when it is clear that we are speaking of strategic planning for and not the planning of research. This calls upon the collective wisdom of all players in the scientific enterprise--academia, government and industry--to find ways to maintain a productive and sound milieu that will nurture scientific creativity and build public trust and support.

Among the topics that we must take into account:

- The NIH budget and its allocation.
- New forms of collaboration with industry.
- The massive research effort against AIDS.
- The question of emphasis on "big science".
- The growing need for trained scientists.
- The use of animals in research
- General concerns over misconduct in science
- The serious need for renovation and replacement of facilities.

## THE BUDGET

It is not uncommon in recent years for members of the scientific community to proclaim that "the sky is falling", that the NIH appropriation has been slashed, that federal support of biomedical research is capricious and the future uncertain.

This does not describe accurately the current state of affairs. Comments of this nature generate unnecessary pessimism.

The past seven years (82-89) have seen a period of sustained growth for the NIH, amounting to 96% in current dollars and 35% in real terms. In each of the last four years, the NIH appropriation has reached a new high in constant dollar terms.

The President's 1990 budget, which I have just finished defending before the House and the Senate, is \$7.5 billion, an increase of 5.3% over the FY 1989 budget. After ruling out the effects of inflation, the budget is

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\*Presentation at the Annual Meeting of the American Society for Microbiology, New Orleans, Louisiana, May 17, 1989.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

essentially stable compared with the average increase throughout the President's budget of 2.7%:

- 25% AIDS
- 3.7% other
- 2.5% increase for genome

Of course, we will not know the congressional response to the 1990 President's budget until later this year. The current services budget for 1990 would be \$8.1 billion which would increase full costs of research project grants, center grants and training grants.

The important point is how much excellent research that budget can support. One way of looking at this is to consider the award rates--that is, the percentage of approved grant applications we are able to fund. In the more than seven years that I have been Director, the overall award rates have been about even--in 1982, 34.7% and in 1989, 35.4%. It is true back in 1975, we were able to fund about 60% of grants eligible for award. The difference today is the increased competition for the money. That is, we are receiving more grant applications--and the cost of the average grant has increased.

Thus, we are holding at about 35-39%. More problematic is the fact that some of the institutes are considerably lower than the NIH overall average.

Furthermore, during the past seven years, we have placed considerable emphasis on minimizing the management of research by others than scientists and on reducing the procedural burdens on investigators. As a result:

The number of research project grants increased from about 16,000 in FY 1982 to almost 21,000 in FY 89.

The proportion of the budget devoted to research project grants increased from 50.3% in FY 1982 to 57.6% in the budget proposed for 1990.

The average length of award of research project grants was increased from 3.3 years in FY 1982 to 4.1 years in FY 1988. The proportion of competing research project grant awards that have a project period for 5 years or more has grown from 19.2% in FY 1982 to 48.3% in 1988.

#### INDUSTRY/GOVERNMENT SUPPORT FOR BIOMEDICAL SCIENCE

In the past decade, important changes have taken place with respect to the support of biomedical research. In 1988, the total national support for health R&D was an estimated \$18 billion. Of that total, 35% was supported by NIH, 42% by industry, and 10% by state, and local governments and private non-profit organizations.

The cross-over year, when industry for the first time surpassed NIH in percent of health R&D support, was 1983.

Yet, when we look at all basic health research support, which totalled some \$5.7 billion in 1987, 62% was provided by NIH and only about 10% by industry.

Breaking down those figures further, by type of effort supported, we find these comparisons: NIH support in 1987 was allocated approximately 61% to basic research, 30% to applied research, and 9% to development. Our internal analysis found a different, but not surprising, trend in industry support: 10% for basic research, and the 90% in application and development.

Clearly, government and industry perform complementary roles in the advancement and application of biomedical knowledge.

It is also important to realize where this money is being spent: of the \$6.9 billion spent for health R&D by industry in 1987 only about \$400 million went to institutions of higher education and other nonprofit organizations such as hospitals and other research institutions as compared with \$5.4 billion from NIH. The bulk of industry support for health R&D, not surprisingly, is spent within the industry itself.

#### ACADEMIA'S TIES WITH INDUSTRY

The advent of the biotechnology industry has stimulated greatly closer ties between industry and academic scientists. Academic scientists, have become increasingly linked with industry--as consultants, members of advisory boards or committees, and sometimes as owners. Many of these relationships are built upon the long-standing encouragement by NIH to commercialize discoveries developed with NIH funds, through patenting and licensing agreements with private industry.

In the early evolution of such academia-industry ties, concerns were expressed about whether such ties would compromise the free flow of scientific interchange or keep discoveries from publication for inordinately long periods. Another concern--for the NIH intramural program as well as for many universities and medical schools--is that ties with industry, which are based on the promise of product development, may compromise the values and mission of the institution and, perhaps, skew research to deemphasize search for fundamental knowledge, or influence hiring decisions.

Another expressed concern is the possibility of conflicts of interest.

June 27 and 28, NIH will hold an open meeting seeking comments from a broad representation of interested individuals and institutions prior to the development of guidelines for NIH grantee institutions. Guidelines may also be considered for advisory boards that monitor clinical trials and for advisory committees participating in peer reviews for NIH.

NIH, of course, is not the only concerned party: many institutions already have some guidelines on conflict of interest in effect for their employees. Scientific societies and university associations are also examining conflict of interest issues, among them the Association of American Universities, the Association of American Medical Colleges, and the American



Association for the Advancement of Science. Furthermore, additional congressional hearings on conflict of interest are planned.

One of the key questions for NIH is not simply what the guidelines referring to conflict of interest actually will be, but who should enforce them. It is the same question of responsibility that would apply to guidelines on protection of human subjects, animal welfare, and misconduct in science. How much responsibility lies with the individual institution and how much should NIH engage in oversight activities?

## TRAINING THE NEXT GENERATION OF RESEARCHERS

### The Distant Future

As mentioned earlier, NIH historically has been committed to training generations of investigators in the life sciences. And, as many of you know, this has been a particular professional interest of mine for many years.

I and many others are concerned about how the biomedical scientific enterprise will maintain the current pace of advance we enjoy today. The seriousness of our predicament was underlined recently in a comment by Dale Corson, president emeritus of Cornell University. In an article on the Nation's technological future that appeared in the Washington Post recently, Dr. Corson stated his opinion that "children are being turned off to science beginning the first day of first grade." He warned that, "The problem is so deep that I think it will take generations to solve." While we can hope that things turn out differently, such a forecast gives notice that the challenge we face is daunting indeed. Perhaps playing into this phenomenon is the anti-intellectualism in our society that does not value or reward the pursuit of knowledge for its own sake.

The Government-University-Industry Research Round Table of the National Academy of Sciences has been exploring issues relating to the identification, recruitment, development, and retention of science and engineering talent. In evaluating the talent pool, the Round Table Group predicts that the demand for scientists and engineers will remain strong in both industry and academia. At the same time, the numbers of Americans in the age groups that normally would be expected to be in training for those careers will be declining.

For example, the current number of 22-year-olds is projected to drop by more than 25% before the end of this century. Even if the current number were not to decline, a significant increase in the proportion of 22-year-olds attaining scientific and engineering degrees would be required to meet the projected research needs.

The Round Table Group estimated that to maintain the 1985 level of potential research trainees into the 1990's the degree award rate would have to increase by 30%. It is estimated that there will be a 30% turnover in academic positions by the year 2000 and that the industry demand for engineers and scientists will increase by 25% in that same period. Unfortunately, the number of undergraduate degrees awarded in the life sciences has decreased steadily since 1977 to the present.

### The Near Future

Regarding more temporally urgent training matters, perhaps of greater personal interest to this group... most of you are probably aware that NIH made the difficult decision earlier this year to increase stipends on the National Research Service Awards to provide a level of support that is adequate to attract the best individuals into biomedical research training. Stipends last were increased in 1985.

Before recommending the increase in stipends, NIH gave this matter careful consideration, fully aware that such an action most likely would result in a reduction in the number of research trainees. There was broad consensus among the NIH leadership that competitive stipend levels must be accorded first priority if the NIH is to continue to attract the best research trainees.

In an internal review, it soon was clear that, absent some special action, some NIH institutes would have no funds available for competing training grants. It was decided to maintain tuition payments for FY 1989 at the FY 1988 level to generate additional savings in the numbers of trainees. The action will permit the support of about 225 additional trainees.

The matter of training the next generation of biomedical scientists is of such concern to me that I have decided to devote a significant portion of my remaining time as NIH Director to it. The time has come for a comprehensive critical look at NIH training programs, including institutional research training grants, fellowships, and research career development awards, to assure the most productive research training effort.

One of three task forces I have set up, under the leadership of Dr. Ruth Kirschstein, will examine the traditional predoctoral and postdoctoral training programs of non-physician scientists, including issues related to stipends and tuition.

Two other task forces are focused on physician-scientist training. I will not discuss this matter in detail with this audience, but will make a few observations about the impact of the downturn in the number of physicians going into research careers upon Ph.D.'s who are still making decisions about career directions.

Recent data have shown that in 1987 (most recent data) medical school clinical departments hired more Ph.D.'s than did basic science departments.

Ph.D.'s with degrees in the life sciences may want to consider adding to their background some exposure to clinically-oriented research.

A recent analysis of a small sample of NIH R01's that were deemed "clinically oriented", showed that half had Ph.D.'s as principal investigators. (10 of 16 in a sample of 1987 records).

## THE HUMAN GENOME PROGRAM

As you know, in FY 1988, NIH received \$17.3 million in new funding for a new research program to map and sequence complex genomes. The President's budget request for FY 1989 increased that amount to \$28 million, with the President's request for FY 1990 at \$100 million. James D. Watson has been recruited to lead the initiative, and planning for the effort is well underway. A stellar group of advisors met for the first time in December, with another meeting scheduled for June.

I am aware that certain misconceptions and anxieties about the Human Genome Program persist among scientists, and I want to address some of these:

Some are concerned that emphasis on the human genome initiative will erode support for other types of basic research. NIH, I think, has indicated that this would not be a healthy occurrence. NIH did not accept the challenge of the human genome project until it was very clear that new money would be forthcoming.

Some are concerned that the human genome program may signal that biomedical science is moving inordinately toward "big science" and that biological scientists will have to join large research groups in order to contribute.

While it is true that some biomedical projects, including some relating to the Human Genome Program, will require interdisciplinary teams, the situation is not likely to mimic the field of physics where scientists are often dependent upon large, hugely expensive equipment. In fact the Human Genome Program--and the data banks of information that will evolve--will make necessary research tools available to a dispersed cadre of interested scientists.

Furthermore, the Human Genome Program--as envisioned by NIH--while it will include some center-type grants, will begin and remain as largely investigator-initiated research effort funded through the research project grant mechanism.

Some additional points of interest to this audience:

The human genome program will include a training component. The idea is not to train an army of mappers and sequencers, but to train Ph.D.-level scientists who can make contributions to the mapping and sequencing effort and also apply their knowledge to biological questions beyond.

Finally with regard to the Human Genome Program, I should make clear that the initiative encourages applications using model organisms such as *e. coli*, *drosophila*, mouse, and yeast, provided the proposed project has relevance to the human genome.



## OTHER ISSUES

### Animals in Research

Now I would like to mention briefly a few other issues that are of concern as we formulate our approach to the challenges of the years ahead.

One such issue is the escalating controversy between the biomedical research community and animal welfare advocates concerning the use of animals in research. This issue, too, carries an inherent strain of anti-intellectualism. Federally supported laboratories have been the targets of illegal break-ins; theft of animals; and destruction of property, equipment and valuable records. The NIH has been the site of a sit-in, prolonged picketing, and two recent demonstrations by animal rights activists.

The introduction of legislation concerning various aspects of animal welfare is increasingly common in Congress and in State legislatures. About one-fourth of the states have enacted legislation prohibiting the release of pound animals for research use.

Eleven bills on different aspects of the care and use of animals in research were introduced in the 100th Congress. Some of them could have severely hindered NIH-funded biomedical research efforts if enacted as proposed.

### RDNA

Although the early history of recombinant DNA technology was fraught with public policy battles adroitly fought and ultimately won by the scientific community, we are not yet out of the woods.

Even though the unfounded fears that accompanied the first applications of genetic manipulations have been laid to rest, an excess of caution has given rise to establishment of barriers that tend to restrict and inhibit international collaboration in this promising area.

It is urgent that policy makers in the United States, as well as in the governments of our trading partners, understand that genetic manipulation should not automatically be equated with increased risk. Added controls imposed simply on the basis of the process used to produce an organism, instead of the characteristics of the product, fly in the face of scientific principles. Such a policy threatens not only modern biomedical research, but in the United States it threatens the vitality of our own biotechnology industry.

Furthermore, similar unfounded fears are likely to require much additional public policy consideration in the areas of human gene therapy and even in connection with the effort to map and sequence the human genome.



### Misconduct in Science

Recently, considerable public attention has been drawn to the issues surrounding what is known as misconduct in science. Although I personally believe that biomedical scientists equal or surpass any other professional group for integrity and high purpose, one must admit that recent substantial examples of dishonesty have severely damaged public confidence in our enterprise.

Misconduct and dishonest behavior in science, though infrequent, are so serious and undermining to the creation of a sound knowledge base in biomedical science that it is of great concern to all participants in research, as well as to the American public.

It is NIH's policy that grantee and contractor institutions receiving NIH research support have the primary responsibility for dealing with possible misconduct involving their scientists. This responsibility includes the duty to conduct inquiries or investigations as appropriate, and to inform and cooperate with NIH as the funding agency.

It is not known whether the incidence of misconduct in science itself has risen within the past decade or so, but it is clear that reports of misconduct have increased in number, requiring NIH to make more explicit the procedures to deal with this phenomenon and to develop ways to prevent such behavior.

Since 1982 NIH has dealt with approximately 100 cases or about 20 per year out of the more than 50,000 scientists who are supported by NIH. In them, the alleged wrongdoing included deliberately deceptive or fraudulent practices, such as fabrication, falsification of data and plagiarism. About one half of reported cases were due to honest errors in judgment or practice, or in some instances scientific disputes.

Grantee institutions have been expanding their efforts during the past several years to monitor, investigate, and report research misconduct involving federal funds, and to promote quality assurance and accountability in the conduct of science. However, there is still a far too prevalent reluctance on the part of universities and other grantee institutions to engage this unpalatable issue. Recent history shows that unless an institution has a well-planned mechanism in place, they will surely mess up when their first misconduct or fraud case occurs.

To provide for more efficient operation on our part, the NIH has recently announced the establishment of an Office of Scientific Integrity (OSI) to see that all PHS policies and procedures related to scientific misconduct are implemented, to monitor the individual investigation into scientific misconduct done by institutions using PHS funds, and, as necessary, conduct its own investigations.

The Office of Scientific Integrity Review (OSIR) has been established in the Office of the Assistant Secretary for Health to review all final reports

of investigations and make final recommendations to the Assistant Secretary for Health on whether any sanctions should be imposed by HHS.

It is essential in dealing with these matters that our efforts to remedy current problems not lead to the development of a vigilante or "ethics cop" mentality with such actions as random unannounced site visits to research labs and data notebook reviews, such as are currently being advocated by some congressional committees.

I hope OSI and OSIR will forestall any such attempts. The Dingell hearings drew scathing press comments. Some media regarded the hearings as a witch-hunt. Even an inquisition, may instill more caution in congressional intrusion into scientific disputes in the future.

### Research Facilities

One last item concerns our nationwide need for research facilities. New scientific discoveries and the development of new technologies are changing the nature of research needs and require more sophisticated facilities to accommodate the new research.

There is also a substantial backlog of needed repair, renovation, and replacement of facilities and equipment. There is also need to meet new requirements for hazardous chemical and biological materials, laboratory animal facilities, handicapped access requirements, and energy conservation requirements.

In 1987 the Congress asked NIH to convene a group of consultants to address the specifics of this serious problem.

The study group, representative of the key leadership of colleges, universities and nonprofit research institutions, met in February last year and not unexpectedly found that there is an urgent need for developing a well-coordinated, long-range national strategy for a research facilities construction program.

The group recommended a 10-year NIH Research Facilities Construction Program, including a 2-year pilot phase to help shape the longer term effort.

The report of the study group has been transmitted to The Congress. We recognize that the issues related to funding these research facilities are complex and embedded in the context of federal fiscal constraints, and that no simple or easy solution is in sight.

There are many other important topics and issues bearing on the long-term health of the biomedical research enterprise that deserve--in fact, demand--our attention as members of the biomedical research community in the Federal Government, in academia, in health care, or in industry.

I have discussed a few key issues today, and time permitting, would be glad to respond to questions or comments.



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# SCIENCE AND THE PUBLIC PROCESS\*

BY

JAMES B. WYNGAARDEN, M.D.\*\*

O I AM GRATEFUL TO HAVE BEEN INVITED TO TAKE PART IN THIS HAPPY OCCASION, AND I DEEPLY APPRECIATE THE GENEROUS WELCOME YOU HAVE GIVEN ME.

ONE OF THE DUTIES OF THE POSITION OF DIRECTOR OF THE NATIONAL INSTITUTES OF HEALTH THAT I HAVE COME TO REGARD AS A VALUABLE FRINGE BENEFIT IS THE EXPERIENCE OF VISITING THE CAMPUSES OF MANY OF AMERICA'S LEADING UNIVERSITIES AND MEDICAL SCHOOLS. SINCE 1982 I HAVE PARTICIPATED IN MORE THAN 75 ACADEMIC CEREMONIES AND SPECIAL OCCASIONS, SUCH AS COMMENCEMENTS, GROUND BREAKINGS, DEDICATIONS, AND STUDENT RESEARCH DAYS. BUT EACH HAS BEEN DIFFERENT, EACH HAS BEEN PLEASANT, AND EACH HAS HAD SPECIAL MEANING TO ME. TODAY IS CERTAINLY NO EXCEPTION. I WAS DELIGHTED THAT THE OCCASION ENABLED ME TO SEE ONCE AGAIN MY LONGTIME FRIEND AND FORMER ASSOCIATE AT DUKE AND AT NIH, DORIS MERRITT, AND MY FORMER BOSS, DR. OTIS BOWEN, WHO WAS SECRETARY OF HEALTH AND HUMAN SERVICES FOR THREE YEARS DURING MY TENURE AT NIH.

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\*PRESENTED AT DEDICATION OF THE MEDICAL RESEARCH CENTER AND LIBRARY BUILDING, UNIVERSITY OF INDIANA SCHOOL OF MEDICINE, INDIANAPOLIS, INDIANA, MAY 20, 1989.

\*\*DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MARYLAND



0 IT IS ALSO A PLEASURE AND AN HONOR TO HAVE A PART IN DEDICATING YOUR "WINDOW TO THE FUTURE." THE ACCOMPLISHMENT IS AN OUTSTANDING EXAMPLE OF WHAT CAN BE DONE THROUGH PARTNERSHIP IN PRIVATE AND PUBLIC FUNDING. THE STATE OF INDIANA, THE UNIVERSITY, AND THE MANY FRIENDS OF THE UNIVERSITY AND ITS SCHOOL OF MEDICINE, INCLUDING MEMBERS OF THE FACULTY, CAN RIGHTLY FEEL GREAT SATISFACTION IN WHAT THEY HAVE DONE TO BRING THIS WORTHY DREAM TO REALIZATION. IT IS INDEED A CAUSE FOR CELEBRATION; AND I OFFER MY HEARTIEST CONGRATULATIONS.

0 YOUR COMMITMENT TO EXCELLENCE IS CLEARLY VISIBLE IN THE MEDICAL RESEARCH CENTER AND LIBRARY. IT IS AN IMPRESSIVE COMPLEX THAT WILL SERVE WELL THOSE WHO STUDY MEDICINE, THOSE WHO PRACTICE MEDICINE, AND THOSE WHOSE RESEARCH IN THE LIBRARY AND IN THE LABORATORIES WILL ADD TO THE BASE OF KNOWLEDGE ON WHICH FURTHER MEDICAL PROGRESS CAN BE MADE. AND THE BENEFITS OF WHAT IS TAUGHT AND WHAT IS LEARNED HERE WILL BE SHARED ACROSS STATE AND NATIONAL BOUNDARIES AND INTO THE NEXT CENTURY.

0 DURING THE PAST FEW MONTHS I HAVE BEEN INVOLVED IN A SERIES OF PUBLIC EVENTS THAT HAVE ILLUSTRATED--IN FACT HAVE CONSTITUTED--DIFFERENT FACETS OF THE SUBJECT THAT I WILL ADDRESS BRIEFLY TODAY. I PLAN TO TALK ABOUT SCIENCE AND THE PUBLIC PROCESS, ABOUT THE AMERICAN PUBLIC IN ITS ROLE AS PATRON OF SCIENCE. IN THIS RELATIONSHIP OUR NATION HAS BEEN

TREMENDOUSLY PRODUCTIVE. ON EVERY HAND WE SEE EXAMPLES OF THE ACCOMPLISHMENTS THAT HAVE RESULTED FROM THE PARTNERSHIPS AMONG THE SCIENTIFIC COMMUNITY, GOVERNMENT, AND PRIVATE INDUSTRY. THIS SUCCESS IS PARTICULARLY EVIDENT IN THE PROGRESS THAT HAS BEEN MADE IN HEALTH CARE AND IN THE PROMISE OF GREAT STRIDES IN THE FUTURE--ALL RESULTING FROM BIOMEDICAL RESEARCH.

0 FROM THE PERSPECTIVE OF DECADES, THE DEVELOPMENT OF THE NATIONAL INSTITUTES OF HEALTH REPRESENTS A REMARKABLE ACCOMMODATION OF THE PUBLIC'S UNDERSTANDABLE DEMANDS FOR RESULTS FROM THE EXPENDITURE OF PUBLIC FUNDS AND SCIENCE'S INHERENT NEED FOR INDEPENDENCE AND ELBOW ROOM. THE LAWS THAT ESTABLISHED AND CONTINUED THE DEVELOPMENT OF THE NIH WERE FARSIGHTED AND PROVED TO BE BENEFICIAL. AND THE DEVELOPMENT AND MATURITY OF THE NIH IN PAST YEARS CAME ABOUT THROUGH THE FORTUITOUS COMBINATION OF TWO ESSENTIAL ELEMENTS--SURE-HANDED AND ENLIGHTENED ADMINISTRATION OF THE CONGRESSIONAL MANDATES ACCOMPANIED BY A TOLERANT CONFIDENCE ON THE PART OF CONGRESS THAT ITS INTENTION WOULD BE HONORED.

0 IT IS AGAINST THIS BACKGROUND THAT I MAKE SOME SUGGESTIONS AS TO HOW EACH OF US--SCIENTISTS, EDUCATORS, GOVERNMENT OFFICIALS, OFFICIALS OF PRIVATE INDUSTRY, AND INTERESTED MEMBERS OF THE GENERAL PUBLIC CAN HELP TO ASSURE CONTINUATION OF THE JOINT EFFORTS THAT HAVE BROUGHT US SO FAR. I THINK THIS NOTE OF CAUTION IS JUSTIFIED BECAUSE IT IS THE NATURE OF

THE SCIENTIFIC ENTERPRISE TO DIFFER FROM MOST OTHER KINDS OF HUMAN ENDEAVOR. AT TIMES CULTURAL CLASHES OCCUR, SOME OF THEM TO THE DETRIMENT OF ALL CONCERNED.

- 0 AMONG THE RECENT PUBLIC EVENTS IN WHICH I HAVE PARTICIPATED WERE THE ANNUAL APPROPRIATIONS HEARINGS FOR THE NATIONAL INSTITUTES OF HEALTH. AT VARIOUS TIMES IN MARCH, APRIL AND EARLY MAY MY COLLEAGUES--THE NIH INSTITUTE AND DIVISION DIRECTORS--AND I APPEARED BEFORE SUBCOMMITTEES OF THE HOUSE AND SENATE APPROPRIATIONS COMMITTEES. OUR PURPOSE IN THESE HEARINGS WAS TO DESCRIBE AND DEFEND THE PRESIDENT'S BUDGET REQUEST FOR NIH FOR FISCAL YEAR 1990.
- 0 WHEN COMPARED WITH MOST OTHER GOVERNMENT AGENCIES, THE NIH HAS FARED WELL IN THE BUDGET PROCESS. IN THE MORE THAN SEVEN YEARS IN WHICH I HAVE BEEN INTIMATELY INVOLVED IN THE DEVELOPMENT, PRESENTATION, AND EXECUTION OF THE NIH BUDGET, IT HAS DOUBLED FROM THE FY 1982 LEVEL OF \$3.6 BILLION TO THE CURRENT OR FY 1989 TOTAL OF \$7.2 BILLION.
- 0 IN THE PAST TWO DECADES THE CONGRESS HAS MADE AN ANNUAL HABIT OF INCREASING THE NIH APPROPRIATIONS OVER THE AMOUNTS REQUESTED BY THE PRESIDENT. IN SOME YEARS THE AMOUNTS ADDED BY THE CONGRESS HAVE BEEN SUBSTANTIAL. BUT COMMON SENSE UNDERScoreD BY SOME STRAWS IN THE WIND CAUTIONS AGAINST COMPLACENCY AT THIS TIME.

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O JOSEPH EARLY, SENIOR MEMBER OF THE APPROPRIATIONS COMMITTEE WHO IS A TRIED AND TRUE FRIEND OF BIOMEDICAL RESEARCH AND OF THE NIH, HAS REMINDED ME REPEATEDLY IN THE PAST FEW YEARS THAT THE TIME IS PASSING WHEN THE CONGRESS BY ALMOST A REFLEX ACTION WILL APPROVE MAJOR INCREASES IN THE BUDGET OF THE NIH.

O WE HAVE BEEN TOLD THAT IN MAKING THE PRESENTATION OF THE NEEDS OF BIOMEDICAL RESEARCH TO THE CONGRESS WE DO NOT ARTICULATE OUR PRIORITIES AS WELL AS OTHER AGENCIES. THE PLURALISTIC AND OPPORTUNISTIC NATURE OF BIOMEDICAL RESEARCH ACTIVITY IS SUCH THAT WE OFTEN MAKE OUR BUDGET PRESENTATION WITH A CONSIDERABLE DEGREE OF UNCERTAINTY AS TO WHERE THE MAJOR ACTION WILL BE.

O MORE CONFUSION IS GENERATED BY THE SPIRITED PRESENTATIONS MADE BY CITIZEN WITNESSES, WHO APPEAR BEFORE THE APPROPRIATIONS COMMITTEES REPRESENTING DOZENS OF VOLUNTARY HEALTH ORGANIZATIONS, EACH ADVOCATING PRIORITY FOR RESEARCH ON PARTICULAR DISEASES OR ORGAN SYSTEMS. SUPPORTIVE GROUPS AND INDIVIDUALS HAVE JOINED IN VARIOUS DELEGATIONS AND COALITIONS TO INFORM THE GENERAL PUBLIC AND THE CONGRESS OF THE NEEDS OF HEALTH RESEARCH PROGRAMS. OFTEN THEY PREPARE ALTERNATIVE BUDGETS FOR CONSIDERATION BY THE CONGRESS. WE WOULD NOT, AND IN FACT COULD NOT, PUT A DAMPER ON THESE HIGHLY SUPPORTIVE CITIZEN GROUPS. THEY HAVE BEEN STAUNCH ADVOCATES OF BIOMEDICAL RESEARCH AND OF THE NATIONAL INSTITUTES OF HEALTH OVER THE YEARS, AND HAVE PLAYED A UNIQUE



AND ESSENTIAL ROLE IN BUILDING OUR NATIONS CAPABILITY TO CONDUCT RESEARCH THROUGH THE INVESTMENT OF THEIR OWN RESOURCES AND THEIR SUPPORT FOR GOVERNMENT FUNDING.

- 0 IN SOME WAYS THE PRESENTATION AND FINAL SHAPING OF THE NIH BUDGET IS A DEMOCRATIC PROCESS WHERE THERE IS A TENDENCY FOR COMPETING VOICES TO CANCEL OUT THE EFFECTIVENESS OF THEIR INDIVIDUAL APPEALS. IN SUCH A CONTEST THE MOST ARTICULATE-- AND POSSIBLY THE LOUDEST--WINS.
- 0 IT IS EASY TO UNDERSTAND WHY THERE IS INCREASING FRUSTRATION ON THE PART OF CONGRESS IN TRYING TO DISCERN WHICH IS THE REAL NIH BUDGET NEED WHEN THEY ARE PRESENTED WITH A NUMBER OF DIFFERENT PROPOSALS HAVING DIFFERENT TOTALS AND SETS OF PRIORITIES. AND ALL THE WHILE THE NIH IS REQUIRED BY THE RIGID ETIQUETTE OF THE BUDGET TO CONFINE ITS PUBLIC STATEMENTS TO SUPPORT OF THE PRESIDENT'S OFFICIAL BUDGET REQUEST, AND TO GIVE ANY ESTIMATES THAT DIFFER FROM IT ONLY UPON DIRECT QUESTIONING BY CONGRESSIONAL COMMITTEES.
- 0 THE IMPORTANCE OF HAVING WELL-ARTICULATED BUDGET PRIORITY IS CONCLUSIVELY ILLUSTRATED BY OUR RECENT EXPERIENCE IN PRESENTING THE HUMAN GENOME INITIATIVE. IT WAS THE FIRST CLEAR PRIORITY PROPOSAL THAT NIH HAD MADE FOR YEARS. IN THIS INSTANCE THE INITIAL FAVORABLE RESPONSE CAME FROM THE ADMINISTRATION, IN FACT FROM WITHIN THE DEPARTMENT OF HEALTH AND HUMAN SERVICES. I AM PLEASED THAT FORMER SECRETARY BOWEN

IS HERE TODAY BECAUSE HIS PRESENCE GIVES ME AN OPPORTUNITY TO EXPRESS ONCE AGAIN MY APPRECIATION FOR HIS STRONG AND TENACIOUS SUPPORT OF THE GENOME PROJECT.

O THE NIH HAS A SPECIAL INTEREST IN THE HUMAN GENOME INITIATIVE BECAUSE WE SUPPLIED MUCH OF THE IMPETUS FOR THE DEVELOPMENT OF THE KNOWLEDGE AND NEW TECHNIQUES THAT MAKE POSSIBLE THE CONSTRUCTION OF HIGH RESOLUTION GENETIC AND PHYSICAL MAPS OF THE TOTAL GENETIC ENDOWMENT OR GENOME, OF ANY ORGANISM OF INTEREST. ULTIMATELY WE EXPECT TO ADVANCE TO A DETERMINATION OF THE COMPLEX SEQUENCE OF THE DNA OF ALL OF THE CONSTITUENT GENES. IN ADDITION TO THE ENORMOUS AMOUNTS OF BIOMEDICAL INFORMATION AND BETTER UNDERSTANDING OF THE ROLE OF GENES IN HUMAN DISEASE THAT WILL COME FROM THIS EFFORT, MANY IMPORTANT SCIENTIFIC AND TECHNOLOGICAL ADVANCES CAN BE EXPECTED, HAVING BOTH BASIC AND COMMERCIAL APPLICATIONS.

O WE HAVE ESTABLISHED AN ORGANIZATIONAL FOCUS TO DIRECT THE PROJECT AND TO COORDINATE IT WITHIN THE NIH, WITH THE NATIONAL CENTER FOR BIOTECHNOLOGY INFORMATION OF THE NATIONAL LIBRARY OF MEDICINE, AND WITH OTHER FEDERAL AND NON-FEDERAL AGENCIES. NOBELIST JAMES D. WATSON ACCEPTED MY INVITATION TO HEAD THE PROGRAM AS THE FIRST NIH ASSOCIATE DIRECTOR FOR HUMAN GENOME RESEARCH. AND I AM DELIGHTED TO REPORT THAT THE PRESIDENT'S BUDGET FOR FISCAL YEAR 1990 PROPOSES THAT \$100 MILLION BE DEVOTED TO THE HUMAN GENOME PROJECT.

- 0 AT THE BEGINNING OF THIS DISCUSSION I NOTED THAT CULTURAL CLASHES HAVE EMERGED THAT CAN AFFECT THE RELATIONSHIPS BETWEEN SCIENCE AND ITS PATRONS. IN REVIEWING BIOMEDICAL RESEARCH IN THE CONTEXT OF THE AMERICAN PUBLIC PROCESS, ONE ENCOUNTERS EMERGING CLASHES THAT HOLD THE POTENTIAL FOR FUTURE DIFFICULTIES OF CONCERN TO THE SCIENTIFIC COMMUNITY AS A WHOLE, AND SPECIFICALLY TO SUCH COMPONENTS OF IT AS THE NATIONAL INSTITUTES OF HEALTH AND THE UNIVERSITY OF INDIANA.
- 0 THE RAPID PACE OF SCIENCE CAN OF ITSELF GENERATE PUBLIC UNEASINESS IF NOT CULTURAL CLASHES. AN EXAMPLE IS THE SET OF SPECTACULAR ADVANCES IN MOLECULAR BIOLOGY THAT PROVIDED THE FOUNDATION FOR THE EMERGENCE OF BIOTECHNOLOGY. IN AN AMAZINGLY SHORT TIME IT HAS BECOME EVIDENT THAT GENETIC ENGINEERING PROVIDES A SAFE AND EFFICIENT PROCESS FOR MANUFACTURING A VAST ARRAY OF DRUGS AND OTHER PHARMACEUTICAL PRODUCTS, FOR CREATING DISEASE RESISTANT PLANTS, AND FOR CLEANING THE ENVIRONMENT. THE POWERFUL NEW METHODS THAT ALLOW INVESTIGATORS TO OBSERVE AND MANIPULATE ORDINARY BIOLOGICAL PROCESSES MAKE IT POSSIBLE TO MAP THE HUMAN GENOME, AND OPEN THE DOOR TO CASCADES OF DISCOVERIES IN THE BASIC AND CLINICAL SCIENCES.
- 0 THE UNFOUNDED FEARS THAT WERE AROUSED IN SOME QUARTERS BY THE THOUGHT OF GENETIC MANIPULATION HAVE BEEN LAID TO REST. BUT THE REMNANTS OF THE EXCESS OF CAUTION HAVE GIVEN RISE TO ESTABLISHMENT OF BARRIERS THAT TEND TO RESTRICT AND INHIBIT

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RESEARCH IN THIS PROMISING AREA. AN ENORMOUS AMOUNT OF TIME AND EFFORT HAS BEEN EXPENDED BY RESEARCHERS AND ADMINISTRATORS AT NIH IN RESOLVING CHALLENGES TO THE USE OF A GENE TRANSFER TECHNIQUE TO LEARN HOW TO IMPROVE A PROMISING NEW KIND OF CANCER TREATMENT.

O THE SAME UNREASONED CAUTION HAS PLACED BARRIERS IN THE PATH OF INTERNATIONAL SCIENTIFIC COLLABORATION. STRICT CONTROLS HAVE BEEN IMPOSED ON THE INTERNATIONAL EXCHANGE OF MATERIALS THAT SEEM TO BE BASED ON EQUATING GENETIC MANIPULATION WITH INCREASED RISK. RESTRICTIONS APPLIED SIMPLY ON THE BASIS OF THE PROCESS USED TO PRODUCE AN ORGANISM, INSTEAD OF THE CHARACTERISTICS OF THE PRODUCT FLY IN THE FACE OF SCIENTIFIC PRINCIPLES. SUCH A POLICY THREATENS NOT ONLY MODERN BIOMEDICAL RESEARCH, BUT ALSO THE VITALITY OF OUR BIOTECHNOLOGY INDUSTRY. AS DIRECTOR OF THE NIH I HAVE BEEN ACTIVE IN INTERNATIONAL EFFORTS TO HARMONIZE THE POLICIES OF COUNTRIES ACTIVE IN BIOMEDICAL RESEARCH SO AS TO MINIMIZE THE NON-TARIFF BARRIERS TO COLLABORATION.

O IN ANOTHER QUARTER, A WELL PUBLICIZED CLASH IS OCCURRING BETWEEN SCIENTISTS CONDUCTING BIOMEDICAL RESEARCH AND A RELATIVELY SMALL BUT ACTIVE MINORITY THAT IN THE NAME OF "ANIMAL RIGHTS" SEEMS DETERMINED TO HALT MUCH IMPORTANT AND VITAL MEDICAL RESEARCH. AN INCREASING NUMBER OF INCIDENTS AROUND THE COUNTRY INVOLVE SENSELESS ACTS OF PROPERTY DESTRUCTION, THEFTS OF ANIMALS, AND IN SOME INSTANCES THE USE



OF TERRORIST TACTICS. THE AMERICAN PEOPLE NEED TO KNOW HOW THE SO-CALLED ANIMAL "RIGHTS" ORGANIZATIONS (AS DISTINGUISHED FROM ANIMAL WELFARE ORGANIZATIONS) HAVE CRIPPLED AND DESTROYED THE PRODUCTIVE WORK OF DEDICATED SCIENTISTS WHO ARE SEEKING BETTER MEASURES FOR THE DIAGNOSIS, TREATMENT, AND PREVENTION OF DISEASE--WORK THAT IN MOST INSTANCES IS SUPPORTED BY THE PEOPLE OF THE UNITED STATES THROUGH THEIR TAX DOLLARS ADMINISTERED BY THE NATIONAL INSTITUTES OF HEALTH.

0 EARLIER IN MY REMARKS I MENTIONED RECENT EVENTS THAT ARE INDICATIVE OF THE CULTURAL CLASHES THAT CAN AFFECT THE FUTURE OF THE SCIENTIFIC ENDEAVOR. ONE SUCH EVENT WAS THE RECENT HEARING BY THE DINGELL COMMITTEE ON ALLEGATIONS CONCERNING THE REPORTING OF RESEARCH IN WHICH ONE OF AMERICA'S MOST PROMINENT SCIENTISTS WAS A CO-AUTHOR. INASMUCH AS SOME OF THE MATTERS INVOLVED IN THIS SITUATION ARE STILL UNDER STUDY, I WILL NOT COMMENT ON THE SUBSTANCE OF THE ISSUES RAISED. HOWEVER, THE RECENT HEARINGS, AS WELL AS OTHERS HELD PREVIOUSLY ON SO-CALLED MISCONDUCT IN SCIENCE, REVEAL THAT WE IN FACT MAY BE WITNESSING A MAJOR CULTURAL CLASH WHERE THE POINTS OF VIEW APPEAR TO BE SO OPPOSED AS TO BE UNRESOLVABLE.

0 WE ARE REVISITING IN A SOMEWHAT DIFFERENT CONTEXT THE SITUATION THAT EXISTED IN THE MID-SIXTIES WHEN THERE WAS A STAMPEDE TO IMPOSE COST-ACCOUNTING, PROFIT AND LOSS MEASURES ON BIOMEDICAL RESEARCH. THE "GREEN EYESHADE" SCHOOL OF

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RESEARCH MANAGEMENT HAD ITS PRINCIPAL EXPRESSION IN THE FOUNTAIN COMMITTEE HEARINGS WELL-REMEMBERED BY ALL "OLD-TIMERS" IN THE BIOMEDICAL RESEARCH COMMUNITY. THE PUBLIC ISSUE THEN WAS FISCAL ACCOUNTABILITY, THE IMPORTANCE OF WHICH IS NOT DEBATABLE. SCIENTISTS, HOWEVER, COULD BE MADE TO APPEAR TO FAVOR FISCAL IRRESPONSIBILITY WHEN THEY PROTESTED THAT CREATIVITY COULD BE STIFLED BY AN ATMOSPHERE OF RIGID RESTRAINT. THE NECESSITY FOR FREEDOM TO FOLLOW SCIENTIFIC CLUES WHEREVER THEY MAY LEAD IS PERFECTLY WELL UNDERSTOOD BY RESEARCHERS, BUT NOT EASILY EXPLAINED IN A POLITICAL FORUM.

0 SIMILARLY, IT IS DIFFICULT TO EXPLAIN THE IMPOSSIBILITY OF IMPOSING A CONTINUOUS SCIENTIFIC AUDIT ON RESEARCHERS AS THEY EXPLORE THE FRONTIERS OF KNOWLEDGE. WITHOUT INTEGRITY SCIENCE IS NO LONGER SCIENCE. BUT IT IS NOT EASY FOR A SCIENTIST TO EXPLAIN THAT ERROR IS A PART OF THE PROCESS OF DISCOVERY AND IS NOT NECESSARILY INCOMPATIBLE WITH INTEGRITY.

0 THE NIH POSITION WITH REGARD TO THE ISSUES OF ACCOUNTABILITY AND SCIENTIFIC INTEGRITY IS TO RECOGNIZE THE SIMPLE FACT THAT THE ONLY WORKABLE PROTECTIONS MUST BE INSTITUTED AND MANAGED BY THE GRANTEE AND CONTRACTOR INSTITUTIONS IN THE CASE OF EXTRAMURAL PROGRAMS, JUST AS WE MUST PROTECT THE INTEGRITY AND ACCOUNTABILITY OF OUR INTRAMURAL PROGRAMS.

0 ANOTHER ISSUE THAT HAS ARISEN OF LATE CONCERNS THE CONFLICTS OF INTEREST THAT MAY ARISE FOR PHYSICIAN SCIENTISTS

PARTICIPATING IN CLINICAL TRIALS. IT IS INCUMBENT ON ALL CONCERNED WITH SUCH TRIALS TO BE ESPECIALLY SENSITIVE TO THE FACT OF AS WELL AS THE APPEARANCE OF CONFLICTS OF INTEREST.

O IT IS AN AXIOM AMONG SUCCESSFUL LOBBYISTS THAT THE MOST EFFECTIVE WORK IN SOLVING CRISES TAKES PLACE BEFORE THE CRISIS ARISES. THERE IS A LESSON THERE FOR ALL OF US. WE NEED TO DEVOTE MORE ENERGY TO UNDERSTANDING THE POLITICAL PROCESS AND CROSS CULTURAL COMMUNICATION DURING THE QUIET TIMES, AND NOT WHEN WE ARE FORCED INTO A DEFENSIVE POSTURE. THE SCIENTIFIC COMMUNITY IS NOTORIOUS FOR NON-PARTICIPATION IN THE PUBLIC DISCUSSION--EVEN OF THE MATTERS THAT THREATEN. WE RECENTLY HAD SURPRISED COMMENTS FROM SOME MEMBERS OF CONGRESS WHEN THEY RECEIVED A FEW LETTERS FROM MEDICAL SCHOOL FACULTY REGARDING THE IMPORTANCE OF ANIMALS FOR RESEARCH. IT WAS NEWSWORTHY WHEN THE MASSIVE FLOOD OF MAIL AGAINST THE USE OF ANIMALS WE RESEARCH CONTAINED A FEW ISOLATED LETTERS ON OUR SIDE OF THE ISSUE.

O AS WE CELEBRATE THE ACCOMPLISHMENT BY THE UNIVERSITY AND THE PEOPLE OF INDIANA THAT THIS CONSTRUCTION REPRESENTS, I PROPOSE THAT AS SCIENTISTS AND EDUCATORS WE CONTINUE OUR CONSTRUCTIVE EFFORTS TO NARROW THE CULTURAL GAPS THAT EXIST. THIS CALLS FOR THE EXERCISE OF SUCH REASONABLE ATTITUDES AS WILLINGNESS TO EXPLAIN AND ACCOUNT FOR THE USE OF PUBLIC FUNDS, AND OUR REDEDICATION TO INTEGRITY, HONESTY, AND OPENNESS IN THE CONDUCT OF OUR HIGH CALLING.

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O I TAKE THE LIBERTY TO PROPOSE THE DEDICATION OF THIS  
IMPRESSIVE MEDICAL RESEARCH CENTER AND LIBRARY BUILDING TO:

O THE FREEDOM OF INQUIRY

O THE NURTURE OF CURIOSITY, AND

O THE JOY OF DISCOVERY.





STATEMENT  
BY  
JAMES B. WYNGAARDEN, M.D.  
DIRECTOR  
NATIONAL INSTITUTES OF HEALTH  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
BEFORE THE  
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY  
HOUSE OF REPRESENTATIVES  
MAY 24, 1989

Mr. Chairman and members of the committee:

I am Dr. James Wyngaarden, Director of the National Institutes of Health. I have been asked to discuss activities by which the National Institutes of Health supports precollege and undergraduate education in science, mathematics, and engineering. At the NIH, in line with our mission, these activities are confined to the biomedical sciences.

The Government-University-Industry Research Round Table of the National Academy of Sciences projects a continuing strong demand for scientists and engineers in the United States but a decline in the numbers of Americans in the appropriate age groups for involvement in these professions. Dale Corson, President Emeritus of Cornell University, recently wrote, "Children are being turned off to science beginning the first day of the first grade." He warned, "The problem is so deep that I think it will take generations to solve."

In connection with its Centennial observance, the NIH began in 1986 to work with other government agencies, academia, and industry to address, more directly, the problem. Those involved have become known as the "Partners in Discovery"--government, academia, and industry. Encouraged by the positive response to our initial efforts, last year I established an advisory group, consisting primarily of NIH Institute Directors, to develop a plan to improve biomedical science education and to attract young people into health research careers. The group will also advise

the Director, NIH, on specific proposals for accomplishing these goals.

Last week, at a meeting of the Advisory Committee to the Director, NIH, representatives from other government agencies, industry, health voluntary and professional organizations, and universities examined recent demographic and sociological trends, assessed their implications for the pool of biomedical researchers, and suggested strategies for sustaining the quality and level of effort of the research.

The message is clear. To maintain the current pace of scientific advancement, and particularly to press forward on such initiatives as biotechnology and the human genome project and the expansion of research on AIDS, we must ensure a continuing supply of bright, well-trained scientists. To accomplish this, we need to attract more young people into the pipeline.

The NIH recognizes the interdependence of science education, research training, and the successful conduct of biomedical research. This linkage provides the opportunity for the development of the next generation of scientists in the same laboratories where new discoveries are being made. NIH provides over \$250 million annually to support approximately 11,000 graduate students and postdoctoral fellows through National Research Service Awards and \$96 million to support about 1,300 additional postdoctoral researchers in Research Career Programs. These research training programs of NIH serve several functions: they attract students to research careers; they enhance research



environments; and most of all, they ensure the nation's research enterprise. The success of these programs, however, ultimately depends on the number of students in primary and secondary education who choose science as a career pathway.

As a means of stimulating the interest of precollege and undergraduate students in the biomedical sciences and health research, I would like to mention a number of the important activities that NIH has undertaken.

#### NIH EDUCATION INITIATIVES

In February 1987, the NIH brought 56 promising high school science students and their teachers to Washington for a special three-day educational program. The students were given an opportunity to chat with 17 Nobel Prize winners, to visit the National Academy of Sciences, to tour the NIH laboratories, and to meet with NIH scientists and physicians. In addition, each student received a special certificate and a \$250 scholarship. Students and scientists alike were most enthusiastic about their experience, and we continue to receive appreciative letters from the students and teachers.

That fall, the NIH opened its doors to Washington area middle school and junior high school students. Approximately 4,000 students from 62 schools visited the NIH Visitor Information Center and the "Discovery Pavilion" where they viewed interactive exhibits provided by groups from NIH, industry, and local government.

### NIH Office of Communications

Every week, two or three school groups tour the NIH and its labs, as well as receive an orientation in the NIH Visitor Information Center aimed at encouraging students to consider careers in biomedical research. In total, over 6,000 students and 300 teachers take part in these visits each year.

In addition, the Office is the NIH Adopt-A-School coordinator for Takoma Park Junior High School that has a magnet science and math program with a mostly minority student population. This permits a continuous round of educational activities and interaction.

### NIH Symposia on Training and Career Opportunities in the Biomedical Sciences

The underrepresentation of minorities in science has exacerbated the problem of ensuring an adequate supply of scientists for future research endeavors. To rectify this, NIH is sponsoring a series of symposia, each targeted to a different minority population. At these meetings, students can talk with scientists and research support personnel who are engaged in a variety of biomedical research careers.

- o The first symposium, held in April 1987, was co-sponsored with the Association of Minority Health Professions Schools (AMHPS) at Meharry Medical College. Using this symposium as a model, AMPHS has sponsored two more symposia with attendance this year of 800-1,000 individuals. NIH has

participated in all the symposia and plans to work with AMHPS to co-sponsor a fourth in the fall of 1990.

- o Last month, NIH and the Indian Health Service sponsored a symposium in Phoenix, Arizona involving the American Indian and Alaska Native communities. Some 200 high school and undergraduate students and their educators heard lectures by representatives of the Public Health Service, academia, and industry. Reaction to this symposium has been highly favorable and we have already met with the IHS to plan the next conference for 1990.
- o A third symposium, involving the Hispanic community, is being planned for this winter in San Antonio, Texas. At that time, we hope to establish stronger ties with the Hispanic community and stimulate interest among its precollege young people in biomedical research careers.

#### Regional Meetings on Recruitment of Minorities to Science Careers

Because data indicate that the next generation of scientists will consist largely of minorities and there is a declining interest of minorities in science careers, NIH is also conducting a series of five regional meetings to solicit testimony from the extramural community regarding the nature and scope of programs to attract and support minorities in biomedical science.

#### Student Curriculum Programs

In late August 1987, the NIH distributed free educational materials to secondary science departments across the country. These materials were designed to accompany a film series to be

aired that October, THE HEALTH CENTURY. NIH distributed a companion volume to high school science departments and libraries throughout the country and to high school teacher recipients of the Presidential Award for Excellence in Science and Mathematics Teaching, sponsored by the White House and administered by the National Science Foundation.

Responses from teachers who received the educational materials on THE HEALTH CENTURY indicated a strong interest in the segment on career pathways. Therefore, NIH, in cooperation with nine private sector companies and the New Jersey Business Industry and Science Education Consortium, is developing a new education curriculum, "Health Careers in the Health Century," to present a broad range of health science career options. The program will be tested early next year in New Jersey with the expectation that it will eventually have nationwide distribution.

In addition, NIH and NASA are collaborating in plans to develop an educational program involving students and teachers in the June 1990 Spacelab Life Sciences I mission.

#### NIH Publications Used in the Schools

Many NIH Institutes publish documents that are used in high schools and colleges. For example, the National Institute of General Medical Sciences has published a series of brochures covering human genetics, cell biology, pharmacology, and structural biology. The most recent brochure, The Structures of Life, was announced in November 1988 through organizations including the National Science Teachers Association. Five



thousand of the 10,000 copies printed have been disseminated; 95 percent are being used in schools.

#### NIH TRAINING AND EDUCATION PROGRAMS

All of the NIH entities participate in government-wide recruitment programs. The Stay-in-School and Summer Aid Programs provide work experience for individuals who need income to remain in school. Many of the students become interested in science by working in the laboratories. Undergraduate students and science majors are employed as laboratory assistants through a variety of employment opportunities.

Most NIH formal training and education programs involving pre-college and undergraduate students target minority groups. These programs include the Minority Access to Research Careers (MARC) Program, which comprises the Honors Undergraduate Research Training Grants and the Faculty Fellowship Awards; the Minority High School Student Research Apprentice Program; the Minority Biomedical Research Support Program; and the Research Grant Supplements for Minority Undergraduate Students.

Under the Honors Undergraduate Research Training Program, administered by the National Institute of General Medical Sciences, 56 minority institutions are receiving support. A congressionally established Task Force on Women, Minorities, and the Handicapped in Science and Technology stated that "of the Federal programs established to give minorities and women access to science and engineering, we found the MARC closest to what we need today . . . a prime example of a successful Federal

intervention program." Other organizations--including the National Science Foundation, the Departments of Energy and Agriculture, and the Sloan Kettering Foundation--are establishing programs in the physical sciences and engineering modeled after MARC.

The MARC Faculty Fellowship Award provides opportunities to strengthen research and teaching programs in the biomedical sciences for students of colleges whose enrollments are drawn substantially from minority groups.

The Minority High School Student Research Apprentice Program, administered by the Division of Research Resources, gives minority teenagers the opportunity to work with biomedical investigators who are committed to broadening their scientific understanding and teaching needed skills.

The academic institutions themselves have come to realize the value of this program in providing students for their own graduate and health professional schools and have matched NIH funds with institutional contributions. Since 1980, when it was established as a Presidential initiative, the program has funded 6,954 summer apprentices.

The Minority Biomedical Research Support (MBRS) Program grant supports a program administrator, student research assistants, and groups of individual research projects at each participating institution. The funds permit faculty members, who frequently have prohibitively heavy teaching loads, to allocate

more of their time to research. Students are given the opportunity to do actual research.

The MBRS Undergraduate Grant enhances research capabilities at 2-year and 4-year colleges that have not been able to secure the resources necessary to support scientific research. The awards are used to support pilot projects, develop research skills, and sponsor other activities to expand faculty and student research capabilities.

The MBRS Program has provided resources for over 90 minority institutions to engage in biomedical research and to update their science curricula. Close to 16,000 students have been involved in research to date and about 80 percent of these are in the pipeline as potential biomedical researchers.

Our newest program, the Research Grant Supplements for Minority Undergraduate Students provides an opportunity for principal investigators of NIH-supported research project grants to hire minority undergraduate students to conduct research in their laboratories for three months, apart from any academic program or affiliation.

Other training programs and efforts to stimulate interest in biomedical science are sponsored by several of the Institutes:

- o The National Cancer Institute sponsors each year a Student Research Training Program that provides training and on-the-job work experience to approximately 90 highly motivated high school and undergraduate students interested in biomedical research.

- o The National Institute of Dental Research conducts outreach activities to encourage junior and senior high school students to consider careers in science. Each year these activities reach over 300 students in four local area high schools.
- o The National Institute of Neurological Disorders and Stroke, through its Outreach Program, provides students with seminars and workshops to familiarize them with the Institute's intramural and extramural programs. The NINDS Summer Program in Neurosciences gives 20-23 academically talented high school and college students a unique opportunity to gain hands-on research training in NINDS laboratories.
- o The National Institute of Diabetes and Digestive and Kidney Diseases supports, each year, the attendance of 10 minority undergraduates at national scientific meetings and provides expanded training opportunities for another 25 outstanding students.
- o The National Institute of Allergy and Infectious Diseases has developed a program, "Introduction to Biomedical Research," that annually brings approximately 50 academically talented students from underrepresented minority groups to NIH to learn about career opportunities in biomedical research, particularly within its intramural program.



NIH estimates that it will spend almost \$50 million in fiscal year 1989 on its educational initiatives and programs, some of which I have described.

NIH, together with its "Partners in Discovery," recognizes the importance of a strong educational system, capable of rejuvenating and supporting teaching of the basic sciences. The framework of scientific thought begins early. If the system is not strong at the beginning, the desired outcome will not be reached.

Biomedical research has never held greater promise for improving the health of the American people. To achieve that promise, NIH will continue to support the development of scientists who have the technical expertise, the theoretical grasp, and the long-range commitment to solving the mysteries of human biology in an environment of stable support. NIH's mandate and resources require us to concentrate on support for advanced education and training so that our investigators can maintain U.S. preeminence in the biomedical sciences. However, we are dependent on the elementary, high school, and college educational systems; we hope that our modest attempts to reach students at these levels will help our Nation address the serious problem of science education and perhaps serve as models for other programs. We join you in exploring new and innovative ways to address the problems we are discussing today.

Thank you, Mr. Chairman. I would be pleased to answer any questions you may have.

# BIOMEDICAL RESEARCH: A FOUNDATION FOR BETTER HEALTH\*

By

James B. Wyngaarden, M.D.\*\*

It is an honor to participate in this International Congress on Public Health and Biomedical Research. And I especially value the opportunity to add my expression of respect and admiration for Professor Francesco Pocchiari--for his fervent leadership--for his knowledge--and for the great enthusiasm with which he worked to improve public health in Italy and throughout the world. It is exquisitely appropriate that this observance of the centennial of Italy's public health law be dedicated to his memory.

I had the pleasure of participating in a symposium hosted by Professor Pocchiari in this place almost exactly five years ago. The meeting was held in celebration of the 50th anniversary of the Istituto Superiore di Sanita. Today, as at the earlier symposium, it is my privilege to represent and bring official greetings from the National Institutes of Health.

There are many close ties between the National Institutes of Health and the Italian scientific community, especially with the scientists at this institution. This collaboration has extended over decades. In years past Professor Pocchiari was a frequent visitor to our offices and laboratories in Bethesda.

The NIH intramural research program attracts talented scientists from around the world, who come to Bethesda to work with our scientists and to share their talents with our researchers. Currently more than 2000 scientists from 76 countries are participating in our visitors and guest researchers programs, with highest representation from Canada, Japan, Italy, the United Kingdom, India, and Israel. During 1988 approximately 200 scientists from Italy worked with our scientists in Bethesda. The Italian contingent was the second largest group of foreign nationals conducting research at NIH.

These programs, over the years, have created an international network of scientists who continue to collaborate with their NIH counterparts throughout their scientific careers.

In addition to these programs the individual research Institutes of NIH all engage in international projects that take advantage of research opportunities wherever they exist. These projects and programs contribute

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\*Presented at the International Congress on "Public Health and Biomedical Research," Rome, Italy, May 29, 1989.

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not only to our scientific knowledge base, but also to improving health in the geographic area of interest.

Among the scientists who have taken part in our visiting program is Maurizio Pocchiari, son of Professor Pocchiari. Maurizio was a visiting fellow at NIH for three years in the early 1980s. He worked with one of our distinguished scientists, Dr. Clarence Gibbs, Jr., in the Laboratory of Central Nervous System Studies of the National Institute of Neurological and Communicative Disorders and Stroke, and since November 1983 has been a collaborator with Dr. Gibbs in studies on the nature of "unconventional viruses."

Before addressing my announced subject, I wish to take a moment to tell you of activities now in planning by the Christopher Columbus Medical Sciences Committee of the NIH with our counterparts in Spain and Italy. The NIH Committee is an affiliate of the Presidential Commission established by the U.S. Congress for the commemoration of the 500th anniversary of Christopher Columbus' 1492 voyage of discovery.

Three international symposia on major health topics will be held as Quincentenary events, co-sponsored by the NIH Committee. The first will be held in Spain in 1990 and the subject will be "Infectious Diseases." In 1991 the second Quincentenary symposium will be held in the United States. The subject will be "Aging and the Quality of Life." The final of the three events appropriately will be held in Genoa in 1992. The subject will be "Biotechnology."

I consider the title of my presentation--"Biomedical Research: Foundation for Better Health"--to be an expression of an established principle. It echoes the one-sentence mission statement of the National Institutes of Health whose purpose, "...is to uncover new knowledge that will lead to better health for everyone."

Currently, nearly two-thirds of NIH's research budget is devoted to studies classed as basic or fundamental. But throughout the agency, there is a strong sense of the relevance of all research to public health. The name of our agency is in itself an expression of the dependent relationship between public health and research. Although our principal function is to conduct scientific research, we are not named the "National Institutes of Biological Research" but the "National Institutes of Health."

American physician-essayist Lewis Thomas has written pointedly on the role of biomedical research as requisite to the ability of public health agencies to carry out their essential functions. He commented, "I believe that the capacity of health departments to deal with their responsibilities will depend directly and almost solely on the quality and scope of biomedical research both basic and applied in the years just ahead."

He went on to make the point that if biomedical research were allowed to languish, we would be required to "make do" with today's scientific information about human disease. "Under these circumstances," he said, "public health departments would be able to continue carrying out such



functions as epidemiology and environmental monitoring but would be able to make only a marginal contribution to the prevention or alleviation of the illnesses contributing the most to the toll of premature death or disability, for the simple reason that we do not understand their causes, the underlying mechanisms by which they run their course, or in most instances how to prevent or cure them."<sup>2</sup>

Throughout the world, new methods are being sought to stem the toll taken by disease and accidents and to curb the inflation of health care costs. Increasing emphasis is being placed on the orientation of biomedical research, health education, and health care services toward the traditional public health goals of disease prevention and health care promotion.

NIH has long been involved in prevention-related research, even though these activities might not always have been termed "prevention." My immediate predecessor as NIH Director, Dr. Donald S. Fredrickson, reported to the U.S. Congress in 1979, that "Our product is knowledge, fundamental knowledge, knowledge about life, disease and malfunction. And our ultimate aim, the aim of all that research, is prevention, because that clearly is the most useful extension of knowledge in the field of health."<sup>3</sup>

Modern prevention research has become more complex, a reflection of a shift in the prevalence of chronic diseases as compared with infectious diseases in the population during the past century. The results experienced, as well as the promise of disease prevention and health promotion in health care, have become more challenging to research scientists throughout the world.

Within the years of the public health century that we are now celebrating, improvements in sanitation brought about a virtual transformation in the health status of major populations through prevention of infectious disease. And in recent years we have broadened these prevention efforts to challenge through basic research the full range of the effects of environmental agents on human health.

In 1988, reports of dying wildlife in poisoned reservoirs and estuaries, sewage washing ashore on popular beaches, contaminated drinking water from agricultural fields, toxic dumps and industrial site runoff, and grim and fanciful descriptions of what life on a "greenhouse" earth may become, have raised the world's awareness of the environment. These reports reinforced the need to answer complex questions about the environment and human health, questions that demand an adequate science base to produce valid answers.

Public health concerns today center on such subjects as ozone--how the thinning of stratospheric ozone may affect human health through increases in exposure to ultraviolet sunlight, and how ozone at ground level is associated with effects on lung function ranging from asthma attacks to increased risk of respiratory illness.



Scientists at the National Institute of Environmental Health Sciences are studying the adverse effects of exposure to lead through lead paint and lead in water systems. Residential radon exposure has been receiving widespread attention. Early on it became apparent that most of our existing information about radon exposure comes from studies of miners with extremely high radon exposures. In addition to involving exposures much higher than those found in the home, studies of miners tend to be limited to healthy males.

Through the years, vaccination has been one of the most powerful and effective tools in public health. Recently it has become possible to study the most fundamental characteristics of the human immune system through the use of colonies of specially bred mice that normally have severe combined immune deficiency (SCID). When human immune cells are injected or transplanted into these mice, investigators have colonies of experimental mice that can be invaluable to better understanding of immune system function.

Vaccine development is a major application of immunologic research. Recombinant DNA technology, nucleic acid sequencing, and peptide synthesis have opened the way for producing highly purified and specific proteins that can be incorporated into vaccines for old and new diseases.

Scientists in laboratories around the world are using the new tools of science to develop or improve vaccines for such infectious diseases as pertussis; infant diarrhea; pneumonia and croup in infants and young children; chlamydia, the most common sexually transmitted disease; and dengue, a major health problem in many areas of the world. Scientists at NIH have been studying the causative agent of Lyme disease since they discovered it in 1982. Lyme disease is the most common arthropod-borne disease in the United States, and our current studies are designed to yield a candidate vaccine in the near future.

The first human tests of an experimental AIDS vaccine have begun and continue in NIH intramural laboratories, as well as in our six external Vaccine Evaluation Units. The vaccine so far has been shown to be safe and immunogenic, but it is not known if it is protective. More studies will have to be done to determine the safest dose that will elicit the maximal immune response.

Yet as we consider the medical advances that have been made or that are in early prospect, we cannot turn aside from the full agenda of unsolved medical problems that continue to exact a fearful physical, mental, and emotional toll on individuals and their families in addition to ever mounting financial burdens accruing to all of society.

More than a decade ago Lewis Thomas first described many measures for treatment of disease as "half-way technologies." The classic illustration of his point was the iron lung that at the time of the polio epidemic in the United States was considered to be a medical advance--a cruel but life saving device. Fortunately, most younger physicians today have had no personal encounter with the use of the iron lung. The need for it

disappeared when Salk and Sabin were able to offer the complete and optimum technology for treating polio by preventing it.

We can hope that later generations of physicians will look back on renal dialysis, on the coronary bypass, on organ transplantation, and many other currently accepted surgical procedures as examples of the iron lung stage in treatment of preventable disease.

The relationship of biomedical research to success in preventing the major killer diseases is clearly illustrated by the search for better ways to prevent or control hypertension. Similarly, the fact that we are part way there in our efforts to control hypercholesterolemia points both to progress and to the need for more progress.

The surest way to prevention of a disease is to understand its nature. One of the promising things about biomedical research today is the rapidity with which we have been gaining knowledge through the use of powerful insights and technologies that have emerged only during the past decade. But, as we learn more we gain a deeper appreciation of what we do not know and how formidable the task of moving beyond halfway technology will be.

In Professor Vincenzo Longo's moving memorial address he spoke of the Professor Pocchiari's international activities and of his philosophy that a process of integration of research activities requires interinstitutional if not international cooperation. This is also a basic tenet of the NIH philosophy toward collaboration in biomedical research.

The history of the battle against AIDS provides a vivid example of the essential role of international collaboration in confronting a difficult biomedical problem and devastating disease entity. The human immunodeficiency virus knows no national boundaries. AIDS has been reported in over 140 countries. Somewhere between 5 and 10 million persons are infected with HIV.

From the beginning of this epidemic, international collaboration has been an essential part of the NIH response. We have worked with scientists from Belgium and Zaire in pioneering studies of the epidemiology of AIDS in Africa since 1983; we have coordinated closely with the WHO Global Program on AIDS; we currently support AIDS research in about 35 countries and plan to spend over \$20 million during the current fiscal year on international AIDS research and research related training. The establishment of an international network for research and training in AIDS will be of immeasurable benefit, both for work on AIDS and other areas of health and disease as well.

Another major endeavor of the NIH that has had a strong international component is the human genome project. In 1982 the NIH, in cooperation with other Federal agencies, created the genetic sequence data bank called GenBank to collect and distribute sequence data to the international scientific community. From the beginning GenBank has collaborated with its counterpart, the European Molecular Biology Laboratory database.

In 1987 scientists in Japan agreed to begin scanning the journals and entering sequence data as well. Now all the databases exchange information regularly so that researchers the world around have access to all available sequences.

We cooperate fully with the Human Genome Organization (HUGO) as an instrument to promote international cooperation and to facilitate collaboration.

Global collaboration is indispensable to the maintenance of excellence in science, and the distinguished panel of speakers at this symposium is symbolic of the common purposes that bind us across oceans and continents literally around the world. These proceedings bear out the truth spoken by Nobelist Jacques Monod when he observed with elegant simplicity, "Science is a country without boundaries."<sup>4</sup>

#### References

<sup>1</sup>Thomas, Lewis, "Biomedical Research and the Future of Public Health," in Health Affairs, Project HOPE, Millwood Va., Winter 1983, p. 34.

<sup>2</sup>Ibid p. 34.

<sup>3</sup>U.S. Congress, House, Committee on Interstate and Foreign Commerce: Future Directions, Hearings before the Subcommittee on Health and the Environment. 96th Congress, 1st Session, 1979, p. 90

<sup>4</sup>Monod, Jacques, Interview in Le Nouvel Observateur, Paris, October 20, 1965, p. 2.

# SCIENTIFIC COLLABORATION--AN ENGINE OF BIOMEDICAL RESEARCH\*

BY

JAMES B. WYNGAARDEN, M.D.\*\*

## INTRODUCTION

I AM VERY GLAD TO BE HERE TODAY TO START OFF TODAY'S DISCUSSION OF COLLABORATION IN BIOMEDICAL RESEARCH. NIH IS INTERESTED IN THIS MATTER FROM A NUMBER OF RELATED PERSPECTIVES.

THIS COUNTRY PLACES ENORMOUS CONFIDENCE IN THE ACADEMIC INSTITUTIONS TO ADVANCE BIOMEDICAL RESEARCH. AN EARLY POLICY STATEMENT, DATING FROM 1945 WHEN NIH'S EXTRAMURAL SUPPORT PROGRAMS BEGAN, HOLDS UP SOLIDLY TODAY. IT READS, "[UNIVERSITIES] ARE THE WELLSPRINGS OF KNOWLEDGE AND UNDERSTANDING. AS LONG AS THEY ARE HEALTHY AND THEIR SCIENTISTS ARE FREE TO PURSUE TRUTH WHEREVER IT MAY LEAD, THERE WILL BE A FLOW OF NEW SCIENTIFIC KNOWLEDGE."

NIH'S COMMITMENT TO ACADEMIC INSTITUTIONS HAS HISTORICALLY GONE BEYOND SIMPLY THE GRANTING OF FUNDS, AND EXTENDS TO SUPPORTING THE INFRASTRUCTURE OF THE ACADEMIC INSTITUTIONS, CONSISTENT WITH OUR CONGRESSIONAL MANDATE. THUS, WE ARE

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CONCERNED WITH THE ENTIRE MILIEU IN WHICH BIOMEDICAL SCIENCE IS CONDUCTED, INCLUDING COLLABORATIVE ARRANGEMENTS THAT LIE AT THE HEART OF THIS ENTERPRISE.

NIH'S INTEREST IN BIOMEDICAL RESEARCH COLLABORATIONS ALSO IS ATTACHED TO OUR STEWARDSHIP ROLE, TO OUR RESPONSIBILITY FOR ASSURING THE CONGRESS AND THE PUBLIC THAT THE APPROXIMATELY \$7 BILLION IN TAX MONIES EXPENDED ANNUALLY FOR BIOMEDICAL RESEARCH THROUGH THE NIH IS WELL SPENT.

WE MUST NOT UNDERESTIMATE THE INTEREST OF THE CONGRESS AND THE PUBLIC IN HOW THIS MONEY IS ALLOCATED AND APPLIED. THE PUBLIC IS ENORMOUSLY INTERESTED IN BIOMEDICAL RESEARCH--CERTAINLY MORE SO THAN IN CHEMICAL OR PHYSICAL RESEARCH--BECAUSE THEY UNDERSTAND THE IMPACT OF OUR ENDEAVOR ON THEIR PERSONAL HEALTH. NO ONE WHO HAS FACED A CONGRESSIONAL OVERSIGHT COMMITTEE ON THE WARPATH COULD UNDERESTIMATE THEIR INTEREST AND INFLUENCE.

TO DATE, THE BIOMEDICAL RESEARCH ENTERPRISE IN THIS COUNTRY HAS BEEN ENORMOUSLY SUCCESSFUL, AND FOR THE MOST PART MAINTAINS THE SUPPORT AND CONFIDENCE OF THE AMERICAN PUBLIC AND THE CONGRESS. I WOULD LIKE TO EXAMINE SOME OF THE ELEMENTS OF THIS ENTERPRISE, PARTICULARLY WITH RESPECT TO COLLABORATIONS, AND COMMENT ON SOME NEW IMPACTS OF RECENT YEARS. I HOPE THAT THIS WILL PROVIDE SOME INSIGHTS FOR THE DISCUSSIONS TO FOLLOW.

## CONVENTIONAL COLLABORATIONS

THE SUCCESS OF THE BIOMEDICAL RESEARCH ENTERPRISE IN THE FORTY SOME YEARS SINCE WORLD WAR II IS BASED LARGELY ON INDIVIDUAL SCIENTISTS WORKING ALONE OR, MORE OFTEN IN MODERN TIMES, ON COLLABORATIONS INVOLVING TWO INDIVIDUALS OR TWO SMALL TEAMS OF SCIENTISTS. SUCH COLLABORATIONS ARE THE SMALL ENGINES THAT DRIVE THE ENORMOUS AND COMPLICATED BIOMEDICAL ENTERPRISE IN THE U.S.

SUCH COLLABORATIONS HAVE BEEN MOST FRUITFUL WHEN EACH PARTY TO THE COLLABORATION HAS BROUGHT SPECIAL EXPERTISE TO BEAR UPON A SELECTED PROBLEM. TRUST HAS ALWAYS BEEN AN IMPORTANT ELEMENT IN A SOLID COLLABORATION, BUT IN GENERAL THIS WAS NOT DIFFICULT TO ASSUME BECAUSE THE CULTURES OF THE COLLABORATORS WERE VERY SIMILAR (USUALLY UNIVERSITY-BASED SCIENTISTS FUNDED BY THE GOVERNMENT OR THROUGH OTHER PUBLIC SUPPORT), AND THEIR MOTIVES WERE SIMILAR: TO ADVANCE SCIENCE; PERHAPS, EVEN MAKE A SEMINAL DISCOVERY; TO PUBLISH THEIR WORK; TO GAIN RECOGNITION FROM THE SCIENTIFIC COMMUNITY; AND, PERHAPS, TO GAIN A COVETED RESEARCH PRIZE. ALTHOUGH SOME SUCH COLLABORATIONS EVENTUALLY LED TO PRACTICAL APPLICATIONS, MOST BEGAN WITH ONLY INTELLECTUAL PURSUIT IN MIND: THE DESIRE TO SOLVE A REALLY IMPORTANT SCIENTIFIC PROBLEM.

PERHAPS THE COLLABORATION BETWEEN WATSON AND CRICK (AS CAPTURED IN WATSON'S BOOK, "THE DOUBLE HELIX") BEST CAPTURES THE

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NATURE OF SUCH PARTNERSHIPS. THE TWO HAD DIFFERENT NATIONAL ORIGINS AND DIFFERENT WORKING STYLES, BUT EACH BROUGHT A DISTINCT EXPERTISE TO SOLVING THE PROBLEM AT HAND--THE STRUCTURE OF DNA. WATSON, THE BIOLOGIST, WHO CALLED HIMSELF A "PHAGE PERSON," AND CRICK, THE X-RAY CRYSTALLOGRAPHER, GAINED MANY BASIC UNDERSTANDINGS TO PUSH THEIR WORK FORWARD THROUGH FREEWHEELING DISCUSSION WITH COLLEAGUES WORKING ON DIFFERENT BUT RELEVANT PROBLEMS. THEY EVEN EXCHANGED DETAILED INFORMATION WITH WILKINS--WHO WAS NOT A COLLABORATOR BUT IN A SENSE A COMPETITOR--ALTHOUGH EVENTUALLY SHARED THE NOBEL PRIZE WITH THEM. COMPETITION WAS AN IMPORTANT INGREDIENT DRIVING THEIR SUCCESS--WATSON AND CRICK WERE CONSTANTLY LOOKING OVER THEIR SHOULDERS AT THE PROGRESS BEING MADE BY LINUS PAULING IN THE U.S.

WE ARE ALL AWARE OF THE INCREDIBLE IMPORTANCE OF THE WORK OF THESE COLLABORATORS: IN 1973, JUST 20 YEARS AFTER THE SOLUTION OF THE STRUCTURE OF DNA BY WATSON AND CRICK, BOYER AND COHEN PERFORMED THE FIRST SUCCESSFUL RECOMBINANT DNA EXPERIMENT. IN 1978, ONLY FIVE YEARS LATER, THE FIRST RECOMBINANT HUMAN INSULIN WAS CREATED. IN 1982, HUMULIN WAS MARKETED, AND TODAY MANY OTHER RECOMBINANT DNA PRODUCTS ARE BEING APPLIED TO TREAT HUMAN DISEASE.

BUT IT IS IMPORTANT TO REMEMBER THAT THE MAJORITY OF THE MOST IMPORTANT ADVANCES IN MEDICINE TO DATE HAVE BEEN BUILT UPON THE WORK OF SCIENTISTS LOOKING NOT FOR APPLICATIONS, BUT FOR

BASIC UNDERSTANDINGS. SUCH EXAMPLES ABOUND IN BIOMEDICAL RESEARCH.

### ROLE OF INDUSTRY IN COLLABORATIONS

HISTORICALLY, BIOMEDICAL RESEARCH IN THIS COUNTRY TOOK A VERY DIFFERENT PATH FROM RESEARCH IN OTHER DISCIPLINES, FOR EXAMPLE, CHEMICAL RESEARCH. IN THE FIELD OF CHEMISTRY, MUCH OF THE SUPPORT OF UNIVERSITY RESEARCH CAME FROM INDUSTRY, MANY UNIVERSITY GRADUATES FOUND EMPLOYMENT IN COMPANIES, AND THERE WERE OFTEN SIGNIFICANT TIES BETWEEN UNIVERSITY FACULTY MEMBERS AND THE INDUSTRIAL SECTOR. THE PATENTING OF NEW CHEMICAL PROCESSES WAS COMMON.

IN CONTRAST, MOST BIOMEDICAL RESEARCH WAS CONDUCTED IN DEPARTMENTS CLOSELY AFFILIATED WITH, OR LOCATED IN, THE NATION'S MEDICAL SCHOOLS. PATENTING OF INVENTIONS ARISING FROM BIOMEDICAL RESEARCH MAINLY OCCURRED IN THE INDUSTRIAL SECTOR. THE ROLE OF NIH AND THE ACADEMIC WORLD INVOLVED IN BIOMEDICAL RESEARCH TRADITIONALLY WAS TO ADVANCE OUR UNDERSTANDING OF THE LIFE SCIENCES, PUBLISH THESE ADVANCES, AND LET THEM FIND THEIR WAY--AS APPROPRIATE--INTO APPLICATIONS OR TANGIBLE PRODUCTS.

WHAT MAY BE PERCEIVED AS A SEA-CHANGE IN INDUSTRY-ACADEMIA-GOVERNMENT RELATIONSHIPS IN BIOMEDICAL RESEARCH IN THE PAST DECADE OR SO HAS BEEN THE RESULT OF A NUMBER OF INTERRELATED OCCURRENCES.



### UNIVERSITIES NEED FOR SUPPLEMENTAL CAPITAL

THE RESEARCH QUESTIONS PURSUED BY BIOMEDICAL SCIENTISTS HAVE BECOME MORE SOPHISTICATED THAN IN THE PAST, REQUIRING MORE COLLABORATIONS ACROSS SCIENTIFIC DISCIPLINES, AND MORE COMPLEX AND COSTLY EQUIPMENT AND FACILITIES. AS A RESULT, UNIVERSITIES HAVE BEGUN SEEKING FUNDING TO SUPPLEMENT GOVERNMENT SUPPORT.

### INDUSTRY SEIZING OPPORTUNITY FOR PROFIT

THE TIME LAG BETWEEN BASIC DISCOVERY AND APPLICATION OR PRODUCT DEVELOPMENT IN BIOMEDICAL RESEARCH HAS SHORTENED. INDUSTRY IS A MAJOR ELEMENT IN THIS QUICKENED PACE, AND THE PHENOMENON IN TURN HAS STIMULATED ADDITIONAL INDUSTRIAL INVOLVEMENT.

THE PROMISE OF BIOTECHNOLOGY IN PARTICULAR HAS HEIGHTENED INDUSTRY'S INTEREST IN MAKING COLLABORATIVE ARRANGEMENTS WITH UNIVERSITY (AND LATER GOVERNMENT) SCIENTISTS.

### PERCEIVED ECONOMIC BENEFITS FOR THE NATION

CONGRESS AND THE ADMINISTRATION HAVE BECOME MORE INTERESTED IN REAPING ECONOMIC BENEFITS FROM OUR LONG-TERM NATIONAL INVESTMENT IN BIOMEDICAL RESEARCH. LAWS FAVORABLE TOWARD INDUSTRY-ACADEMIA-GOVERNMENT RELATIONSHIPS HAVE BEEN PASSED, FOR

EXAMPLE, THE TECHNOLOGY TRANSFER ACT OF 1986 AND THE EARLIER ORPHAN DRUG ACT.

THE EXTENT AND NATURE OF INDUSTRY SUPPORT OF BIOMEDICAL RESEARCH

IN EXAMINING THESE "NEW" FORMS OF COLLABORATION IN BIOMEDICAL RESEARCH--THOSE INVOLVING INDUSTRY, IT MAY BE IMPORTANT TO LOOK AT THE BIGGER PICTURE OF U.S. SUPPORT FOR HEALTH R&D.

IN 1988, THE TOTAL NATIONAL SUPPORT FOR HEALTH R&D WAS AN ESTIMATED \$18.13 BILLION. OF THAT TOTAL, 35% WAS SUPPORTED BY THE NIH, 42% BY INDUSTRY AND 10% BY STATE AND LOCAL GOVERNMENT AND BY PRIVATE NON-PROFIT ORGANIZATIONS.

THE CROSS-OVER YEAR, WHEN INDUSTRY FOR THE FIRST TIME SURPASSED NIH IN PERCENT OF HEALTH R&D SUPPORT, WAS 1983.

YET, WHEN WE LOOK AT ALL BASIC HEALTH RESEARCH SUPPORT, WHICH TOTALLED SOME \$5.7 BILLION IN 1987, 62% WAS PROVIDED BY NIH AND ONLY ABOUT 10% BY INDUSTRY.

BREAKING DOWN THOSE FIGURES FURTHER, WE FIND THESE COMPARISONS: NIH SUPPORT IN 1987 WAS ALLOCATED APPROXIMATELY 61% TO BASIC RESEARCH, 30% TO APPLIED RESEARCH, AND 9% TO DEVELOPMENT. OUR INTERNAL ANALYSIS FOUND A DIFFERENT, BUT NOT

SURPRISING, TREND IN INDUSTRY SUPPORT: 10% FOR BASIC RESEARCH, AND 90% IN APPLICATION AND DEVELOPMENT.

CLEARLY, GOVERNMENT AND INDUSTRY PERFORM COMPLEMENTARY ROLES IN THE ADVANCEMENT AND APPLICATION OF BIOMEDICAL KNOWLEDGE.

IT IS ALSO IMPORTANT TO REALIZE WHERE THIS MONEY IS BEING SPENT: OF THE \$6.9 BILLION SPENT BY INDUSTRY IN 1987 ONLY ABOUT \$400 MILLION WENT TO INSTITUTIONS OF HIGHER EDUCATION AND OTHER NONPROFIT ORGANIZATIONS SUCH AS HOSPITALS AND INDEPENDENT RESEARCH INSTITUTIONS. THIS CAN BE COMPARED WITH \$5.4 BILLION FROM NIH TO THESE SAME RECIPIENTS. THUS THE INDUSTRY CONTRIBUTION IS ONLY 7% THAT OF THE NIH. THE BULK OF INDUSTRY SUPPORT FOR HEALTH R&D, NOT SURPRISINGLY, IS SPENT WITHIN THE INDUSTRY ITSELF.

INDUSTRY IMPACT AS COMPARED WITH GOVERNMENT IMPACT CAN BE LOOKED AT IN ANOTHER WAY--FROM THE PERSPECTIVE OF JUST ONE UNIVERSITY. THE WISCONSIN ALUMNI RESEARCH FOUNDATION (WARF), IS AN INDEPENDENT FOUNDATION ORGANIZED TO ADMINISTER PATENTS AND LICENSES RESULTING FROM RESEARCH DISCOVERIES BROUGHT TO IT BY UNIVERSITY OF WISCONSIN FACULTY MEMBERS AND TO APPLY THAT INCOME TO FUND FURTHER RESEARCH AT THE UNIVERSITY. IN THE YEAR 1984-1985, WARF BROUGHT IN \$7.2 MILLION OR 3.6 PERCENT OF A \$200 MILLION RESEARCH BUDGET, WHILE IN A COMPARABLE TIME PERIOD, NIH PROVIDED \$58 MILLION TO THE UNIVERSITY OF WISCONSIN SYSTEM.

## A CLOSER LOOK AT INDUSTRY COLLABORATIONS

ALTHOUGH THE TOTAL AMOUNT OF MONEY INVESTED BY INDUSTRY IN ACADEMIC INSTITUTIONS MAY PALE IN COMPARISON WITH GOVERNMENT CONTRIBUTIONS, IT IS IMPORTANT FOR ALL CONCERNED--GOVERNMENT, ACADEMIA, AND INDUSTRY TO FOCUS SOME ATTENTION IN THIS DIRECTION.

ALL OF US ARE FAMILIAR WITH THE QUESTIONS SURROUNDING SUCH RELATIONSHIPS--QUESTIONS THAT ARE RAISED PRIMARILY BECAUSE THESE NEW COLLABORATIONS DIFFER IN SEVERAL RESPECTS FROM THE WATSON-CRICK TYPE COLLABORATIONS MENTIONED EARLIER.

THE PRIMARY DIFFERENCE IS THAT THE "NEW" COLLABORATIONS ARE BASED ON DEVELOPING A PRODUCT, AND THE EXPECTATION THAT THE PRODUCT WILL YIELD PROFITS. WHILE THERE IS NOTHING INHERENTLY WRONG WITH THE PROFIT MOTIVE, INDEED, THIS COUNTRY HAS BEEN ENERGIZED BY THAT DRIVING FORCE, IT MEANS THAT A NEW MOTIVE HAS BEEN ENTERED INTO THE COLLABORATIVE EQUATION.

COLLABORATION BETWEEN INDUSTRY AND ACADEMIC (OR GOVERNMENT SCIENTISTS) MEANS THAT TWO CULTURES WITH DIFFERENT MOTIVES AND PHILOSOPHIC AND OPERATIONAL TRADITIONS HAVE COME TOGETHER. ANY EFFORT TO GUIDE THESE COLLABORATIONS BECOMES A BALANCING ACT OF OFTEN COMPETING INTERESTS.

IN MY VIEW, THESE NEW ARRANGEMENTS FROM THEIR OUTSET SHOULD BE BUILT--LIKE THOSE OF EARLIER YEARS--UPON THE SPECIAL EXPERTISE



BROUGHT TO THE COLLABORATION BY EACH MEMBER. THEY SHOULD BE AIMED AT FULFILLING THE MISSION OF THE INSTITUTION ITSELF, NOT AT ANSWERING THE IMPERATIVE OF INDUSTRY. CONCERNS ABOUT THE STIFLING OF FREE AND OPEN DISCUSSION AMONG COLLEAGUES AT THE INSTITUTION NOT INVOLVED IN THE INDUSTRY COLLABORATION, AND ABOUT PROMPT PUBLICATION ARE REAL. THESE ARE MATTERS THAT REQUIRE ATTENTION FROM SCIENTISTS, INSTITUTIONS, AND PROFESSIONAL ASSOCIATIONS SUCH AS AAU AND AAMC.

OTHER QUESTIONS FOR THE INSTITUTIONAL ADMINISTRATION INCLUDE: WILL THESE NEW COLLABORATIONS WITH INDUSTRY LEAD TO A SHIFTING OF THE RESEARCH MISSION (FROM PRIMARILY DISCOVERY TO PRIMARILY DEVELOPMENT)? WILL THEY CAUSE A CHANGE IN THE KINDS OF RESEARCH EXPOSURE AFFORDED TO STUDENTS? WILL THEY IMPACT HEAVILY UPON HIRING AND PROMOTION DECISIONS? WILL ACADEMIC SCIENTISTS LOSE THEIR IDENTITY FOR THE PUBLIC AS UNBIASED EXPERTS?

ALL OF THESE QUESTIONS MAY BE SEEN AS MATTERS IMPACTING ON THE RESEARCH CULTURE, AND ALTHOUGH NIH IS INTENSELY CONCERNED ABOUT HOW THESE ARE DEALT WITH AT UNIVERSITIES AND MEDICAL SCHOOLS, THERE IS LITTLE THAT NIH CAN DO TO INFLUENCE THEM. THEY LARGELY REMAIN IN THE PURVIEW OF THE INDIVIDUAL INSTITUTIONS.

A SECOND TYPE OF CONCERN RELATES TO CONFLICT OF INTEREST--A MATTER WHERE NIH DOES HAVE A DIRECT ROLE TO PLAY WHEN INDUSTRY AND NIH/ADAMHA FUNDS ARE BOTH INVOLVED IN SUPPORT OF ACADEMIC INVESTIGATORS.

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LATER THIS MONTH, NIH WILL HOLD AN OPEN MEETING SEEKING COMMENTS FROM A BROAD REPRESENTATION OF INTERESTED INDIVIDUALS AND INSTITUTIONS PRIOR TO THE DEVELOPMENT OF GUIDELINES ON CONFLICT OF INTEREST FOR NIH GRANTEE INSTITUTIONS.

ONE OF THE KEY QUESTIONS FOR NIH IS NOT SIMPLY WHAT THE GUIDELINES REFERRING TO CONFLICT OF INTEREST ACTUALLY WILL BE, BUT WHO SHOULD ENFORCE THEM. IT IS THE SAME QUESTION OF RESPONSIBILITY THAT WOULD APPLY TO GUIDELINES ON PROTECTION OF HUMAN SUBJECTS, ANIMAL WELFARE, AND MISCONDUCT IN SCIENCE. HOW MUCH RESPONSIBILITY LIES WITH THE INDIVIDUAL INSTITUTION AND HOW MUCH SHOULD NIH ENGAGE IN OVERSIGHT ACTIVITIES?

NIH, OF COURSE, IS NOT THE ONLY CONCERNED PARTY: MANY INSTITUTIONS ALREADY HAVE SOME GUIDELINES ON CONFLICT OF INTEREST IN EFFECT FOR THEIR EMPLOYEES. SCIENTIFIC SOCIETIES AND UNIVERSITY ASSOCIATIONS ARE ALSO EXAMINING CONFLICT OF INTEREST ISSUES, AND ADDITIONAL CONGRESSIONAL HEARINGS ARE PLANNED.

#### COORDINATED RESEARCH EFFORTS/"BIG SCIENCE" UNDERTAKINGS

ANOTHER PERCEIVED NEW TYPE OF COLLABORATIVE EFFORT IN BIOMEDICAL RESEARCH MIGHT BE DESCRIBED AS COORDINATED RESEARCH OR IN THE VERNACULAR, "BIG SCIENCE"--WHERE A CLEAR GOAL IS RECOGNIZED AND A MAJOR CHALLENGE LIES IN COORDINATING NATIONALLY THE VARIOUS ELEMENTS THAT MUST COME TOGETHER TO SOLVE THE PROBLEM

AT HAND, MINIMIZING DUPLICATION OF EFFORT AND RECOGNIZING AND FILLING GAPS.

ALTHOUGH SUCH COORDINATED RESEARCH HAS BEEN SEEN IN THE PAST IN BIOMEDICAL RESEARCH--NOTABLY WITH THE CANCER VIRUS PROGRAM AND THE DRUG DEVELOPMENT PROGRAMS IN CANCER--THIS KIND OF RESEARCH ARRANGEMENT HAS RECENTLY COME INTO PROMINENCE THROUGH THE NIH AIDS RESEARCH PROGRAM AND THE NIH HUMAN GENOME RESEARCH PROGRAM.

IN THE FORMER, THE NEED FOR MASSIVE RESOURCE ALLOCATION AND CENTRAL COORDINATION WAS STIMULATED BY A CRITICAL PUBLIC HEALTH EMERGENCY--AIDS--AND IN THE LATTER WAS DRIVEN BY THE UNPRECEDENTED SCIENTIFIC OPPORTUNITY PRESENTED TO MAP AND SEQUENCE THE ENTIRE HUMAN GENOME. BOTH OF THESE EFFORTS REQUIRE PARTICIPATION FROM FOREIGN AND DOMESTIC SCIENTISTS AND INSTITUTIONS AND INVOLVE SCIENTISTS FROM ACADEMIA AND INDUSTRY.

THE NIH AIDS EFFORT IS MANAGED BY A NEW ORGANIZATION WITHIN THE NIH--THE OFFICE OF AIDS RESEARCH--HEADED BY DR. ANTHONY FAUCI--WHILE THE NIH HUMAN GENOME RESEARCH PROGRAM IS HEADED BY DR. JAMES WATSON.

NIH HAS ENLISTED NUMEROUS TALENTED SCIENTISTS IN ACADEMIA, INDUSTRY AND GOVERNMENT IN AN INTENSIVE MULTIDISCIPLINARY EFFORT TO DEVELOP AIDS DRUGS, WHICH INCLUDES LARGE-SCALE SCREENING OF EXISTING COMPOUNDS AND A NATIONWIDE CLINICAL TRIALS NETWORK TO EVALUATE DRUGS. THE PROGRAM INCLUDES A NETWORK OF VACCINE

DEVELOPMENT UNITS AND--ADDED TO FILL A PERCEIVED GAP--A GROUP OF PROJECTS AIMED AT THE RATIONAL CREATION OF CANDIDATE DRUGS BASED ON STUDIES IN STRUCTURAL BIOLOGY.

THE HUMAN GENOME RESEARCH PROGRAM HAS NOT YET DEVELOPED ITS FINAL, DETAILED ACTION PLAN FOR REACHING ITS GOAL. IT IS A FORMIDABLE TASK FOR ANY ORGANIZATION TO DETERMINE JUST HOW TO DIVIDE OUT RESPONSIBILITY FOR VARIOUS ASPECTS OF THE PROJECT--DEVELOPING TECHNOLOGY AND DATABASE CAPABILITY, MAPPING AND SEQUENCING--AND TO MOBILIZE THE BIOMEDICAL RESEARCH COMMUNITY SO THAT ALL THE NECESSARY ELEMENTS ARE ATTACKED IN A LOGICAL, TIMED ORDER.

I MENTION THESE TWO PROJECTS PARTICULARLY BECAUSE THEY HAVE LEAD TO CERTAIN MISCONCEPTIONS AND ANXIETIES WITHIN THE BIOMEDICAL RESEARCH COMMUNITY. SOME ARE CONCERNED THAT EMPHASIS ON THE HUMAN GENOME INITIATIVE AND THE COORDINATED AIDS INITIATIVE WILL ERODE THE LONG-STANDING NIH SUPPORT FOR TRADITIONAL COLLABORATIONS IN BIOMEDICAL RESEARCH--INVESTIGATOR-INITIATED PROJECTS. THIS VIEW IS UNDULY PESSIMISTIC. NIH DID NOT ACCEPT THE CHALLENGE OF THE HUMAN GENOME PROJECT UNTIL IT WAS VERY CLEAR THAT CONGRESS INTENDED TO ADD NEW MONEY FOR THIS TO THE NIH BUDGET. IN ADDITION, NIH HAS ALWAYS MADE CLEAR THAT EMPHASIS ON AIDS RESEARCH SHOULD NOT BE AT THE EXPENSE OF OTHER IMPORTANT WORK. FURTHERMORE, IT IS ENVISIONED THAT THE AIDS PROGRAM AND THE HUMAN GENOME PROGRAM WILL ALWAYS INCLUDE A LARGE PORTFOLIO OF INVESTIGATOR-INITIATED BASIC RESEARCH GRANTS.



I DO NOT BELIEVE THAT BIOLOGICAL SCIENCE WILL MOVE IN THE DIRECTION TAKEN BY PHYSICS. WHILE IT IS TRUE THAT SOME BIOMEDICAL PROJECTS, INCLUDING THOSE RELATING TO THE HUMAN GENOME PROGRAM, WILL REQUIRE INTERDISCIPLINARY TEAMS, THE SITUATION IS NOT LIKELY TO MIMIC THE FIELD OF PHYSICS WHERE SCIENTISTS ARE OFTEN DEPENDENT UPON LARGE, EXPENSIVE EQUIPMENT--AND THEREFORE TEND TO WORK IN LARGE TEAMS ON VERY EXTENSIVE PROJECTS.

#### SUMMARY COMMENTS

IN SUMMARIZING MY COMMENTS, I WANT TO REITERATE THE IMPORTANCE OF CONTINUED EMPHASIS ON SUPPORT OF BASIC RESEARCH AND UNDERLINE THE VITAL ROLE THAT ACADEMIA-BASED SCIENTISTS MUST CONTINUE TO PLAY IN THAT MOST CREATIVE AND VALUABLE UNDERTAKING. INDUSTRY COLLABORATIONS WITH ACADEMIC AND GOVERNMENT SCIENTISTS CAN BE FRUITFUL TO ALL PARTIES CONCERNED--INCLUDING THE PUBLIC--BUT THEY SHOULD NEVER GROW SO PERVASIVE AS TO DISTRACT THE ACADEMIC INSTITUTION OR GOVERNMENT LABORATORIES FROM THEIR TRADITIONAL ROLES.

MANAGED, "BIG SCIENCE" PROJECTS HAVE A PLACE IN MODERN SCIENCE, BUT SUCH VENTURES SHOULD BE LIMITED TO A VERY FEW, CRITICAL NEEDS OR OPPORTUNITIES SUCH AS THE COORDINATED AIDS PROGRAM AND THE HUMAN GENOME PROGRAM. IT MUST BE MADE CLEAR TO THE CONGRESS THAT THE OVERWHELMING PROPORTION OF GOVERNMENT FUNDS FOR BIOMEDICAL RESEARCH SHOULD BE RESERVED FOR INVESTIGATOR-

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INITIATED BASIC RESEARCH IF THE ENTERPRISE IS TO CONTINUE ITS SUCCESSES INTO THE FUTURE.

WITH REGARD TO COLLABORATIONS BETWEEN INDUSTRY AND ACADEMIC SCIENTISTS, THE PRIMARY RESPONSIBILITY FOR INTEGRATING THIS NEW ELEMENT INTO THE BIOMEDICAL RESEARCH ENTERPRISE LIES WITH THE ADMINISTRATION OF THE ACADEMIC INSTITUTIONS. THEY MUST FIND WAYS TO TAKE ADVANTAGE OF THE OPPORTUNITIES AFFORDED BY THE INFUSION OF INDUSTRY'S RESOURCES WITHOUT COMPROMISING THE VALUES AND MISSION OF THE UNIVERSITY.

GUARDING THE INTEGRITY OF THE INDIVIDUAL INSTITUTION AND ACADEMIA IN GENERAL IS ALSO A FIRST-LINE RESPONSIBILITY FOR UNIVERSITY ADMINISTRATORS AND THEIR PROFESSIONAL ASSOCIATIONS. EVEN A FEW CASES OF SERIOUS CONFLICT OF INTEREST OR SELF-DEALING ON THE PART OF ACADEMIC SCIENTISTS CAN BE SEVERELY DAMAGING IN TODAY'S CLIMATE. I BELIEVE WE HAVE SEEN IN RECENT YEARS AN UPSURGE OF ANTI-INTELLECTUALISM IN THIS COUNTRY (AND PERHAPS IN OTHER WESTERN NATIONS) THAT HAS POTENTIAL FOR ERODING THE PUBLIC SUPPORT OF BIOMEDICAL SCIENCE. THIS IS EVIDENCED BY THE STRONG ANIMALS RIGHTS MOVEMENT, AND BY LOWER PITCHED BUT CONTINUED PUBLIC POLICY BATTLES RELATING TO RECOMBINANT DNA RESEARCH.

RECENT HEARINGS ON MISCONDUCT IN SCIENCE, FOCUSSED ON BIOMEDICAL RESEARCH, HAVE DISCLOSED A MAJOR CULTURAL CLASH BETWEEN THE CONGRESS AND THE SCIENTIFIC COMMUNITY. WE NEED TO PAY MORE ATTENTION TO THESE STORM CLOUDS WITH REGARD TO CONFLICT

OF INTEREST ISSUES. WE NEED TO WORK TOWARD REGAINING PUBLIC TRUST IN THE BIOMEDICAL RESEARCH COMMUNITY.

SCIENTISTS MUST MAKE A GREATER EFFORT TO LEARN MORE ABOUT THE POLITICAL PROCESS AND MUST WORK WITH THEIR UNIVERSITY ADMINISTRATORS--NOT JUST IN A TIME OF CRISIS--TO FIND WAYS OF RESOLVING WHAT MAY APPEAR AS A CONFLICT BETWEEN FREEDOM OF INQUIRY AND THE WILLINGNESS TO ACCOUNT FOR THE USE OF PUBLIC FUNDS.

WE--THE NIH AND THE ACADEMIC COMMUNITY--NEED TO ACT EARLY IN ORDER TO FORESTALL THE IMPOSITION OF GUIDELINES, RULES AND REGULATIONS THAT MAY PROVE UNWORKABLE TO THE CREATIVE, SCIENTIFIC ENTERPRISE.

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STATEMENT

BY

JAMES B. WYNGAARDEN, M.D.

DIRECTOR

NATIONAL INSTITUTES OF HEALTH

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

HOUSE GOVERNMENT OPERATIONS SUBCOMMITTEE

ON

HUMAN RESOURCES AND INTERGOVERNMENTAL RELATIONS

U.S. HOUSE OF REPRESENTATIVES

JUNE 13, 1989



Thank you very much, Mr. Chairman, for providing this opportunity to discuss with the Committee the actions the Public Health Service has taken regarding the issue of conflict of interest in research, and our intentions for the future. The remarkable biological revolution of the past 20 years has led to research relationships among industry, academic and Government scientists on a scale new to biomedical science in the United States. Although, for the most part, such relationships have been positive, nevertheless they emphasize the need to ensure the impartiality of research results and the integrity of the environment in which research is conducted.

The complex relationships among Government, universities, and industry mean that we need to pay thorough attention to standards of conduct in research sponsored by the PHS. Such research, with its direct impact on the health of the people of this nation, must be free from any untoward influences. At the same time, we must preserve the fragile balance between innovation, industry involvement, and the proper stewardship of Federal funds.

For many years, the Public Health Service grants policy has required that recipient organizations establish safeguards to prevent employees, consultants, or members of governing bodies from using their positions for private financial gain for themselves, for family members, or others with whom they have business ties. Therefore, each institution receiving PHS financial support must have written policy guidelines on conflicts of interest and their avoidance. These guidelines must indicate the conditions under which outside activities, relationships, or financial interests are proper or improper, and provide for notification of these kinds of activities, relationships, or financial interests to responsible and objective institution officials. Although such institutional guidelines need not be formally submitted to, or approved by, PHS awarding components, they must be available for review upon request.

To determine the scope of institutional guidelines, last November we requested our top 20 grantees to submit copies of their conflict of interest policies and procedures to the NIH. Analyses of the responses showed wide variation in scope and detail. All of the guidelines rely on disclosure to some higher level in the institutional hierarchy. However, decisions on what activities should be disclosed, and when, are not always clearly defined. One third of the policies did not mention stock holdings or financial interest in companies related to the faculty member's research. Five had thresholds for reporting of stocks and other financial interest, which ranged from \$1,000 to \$25,000.

In the January 20, 1989, issue of the NIH Guide for Grants and Contracts, NIH and ADAMHA invited comments regarding avoiding conflicts of interest on the part of extramural researchers. We stated that "NIH expects that participating investigators and consultants will not have financial interests in organizations or entities that produce drugs, devices, or other interventions studied in a [PHS-sponsored] controlled clinical trial." We also indicated our intent to develop appropriate guidance for such relationships. However, we stated that these guidelines should not impede research, development, or testing under NIH awards specifically mandated in the Congressionally established Small Business Innovation Research program.

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Although PHS guidelines must be flexible enough to allow for differences in institutional governance, we must articulate clearly the standards that all institutions must meet to be eligible to receive PHS funds. The NIH proposes that these standards start with assurance to appropriate institution officials and to NIH that researchers have no financial interests in organizations whose products they will test. Financial interest would include equity positions, stock ownership or stock options, board membership, consultantships or other significant financial or professional relationships. However, it would also be important to provide for a mechanism that would take into consideration special circumstances that warrant limited exceptions where the financial intent or relationship would clearly not affect the individual research.

Thus the NIH and the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) plan to develop appropriate guidelines for all awardee organizations to adopt and implement for avoiding conflicts of interest on the part of their researchers, consultants, and other participants in PHS-awarded projects. To this end, the NIH and ADAMHA will hold a two-day conference on June 27-28, to provide an opportunity for discussion of conflict of interest issues with the research community. Topics will include the application of conflict of interest principles in biomedical research from university, industry, congressional, and Federal perspectives. Other issues involve establishment of for-profit subsidiaries by universities, industry large-scale research support to universities, and responsibilities for oversight. We anticipate broad discussion on questions such as:

- When, if ever, might ownership of a commercial research enterprise or involvement in a research business venture not constitute a conflict of interest with one's government-sponsored research?
- Will a researcher's financial interest, stock ownership, agreement with equipment manufacturers, etc., necessarily influence research results?
- How should consultantships to industry, including payment of honoraria for speaking at industry-sponsored meetings, be treated?
- Should researchers be permitted to benefit financially from information obtained in the course of research?

We anticipate a comprehensive and stimulating exchange. Following this conference, we will develop proposed guidelines defining the scope of and standards for conflict of interest policies, procedures for disclosure, and remedies and sanctions that will apply to grantee, contractor, and applicant institutions. We will publish these proposed guidelines in the NIH Guide for Grants and Contracts for consideration and comment by our broad constituency of biomedical researchers and administrators. As I mentioned earlier, we expect from the onset that these guidelines will require that institutions bear the first line responsibility for ensuring that their researchers and other staff avoid conflicts of interest.

The NIH has also acted to meet similar problems and competing interests faced within its intramural research program. In 1985, NIH amended its policy on outside work to permit NIH scientists to consult for industry. With the

advent of the Federal Technology Transfer Act in 1986, which authorized collaborative research projects between our scientists and industry, we barred our scientists from simultaneous consulting and collaboration relationships with a company. To identify and evaluate potential conflicts of interest, the NIH-ADAMHA Patent Policy Board held a retreat last December to discuss the complex issues raised by interrelations between NIH intramural scientists and industry. The summary report from that meeting is serving as the basis for an expanded analysis of conflicts of interest now being conducted by the NIH Office of Invention Development.

The PHS is concerned about maintaining the integrity of science. We believe that protection of that integrity must be a joint effort on the part of the Government and the institutions where research is performed. The new and evolving interactions among academia, industry, and government create a new imperative for systematic examination of all issues for possible conflict of interest. We must ensure that research results are not distorted by financial involvements of investigators, but we must also ensure that the progress of science is unhindered.

I believe that it is the responsibility of institutions receiving Federal funds for research to adopt and enforce policies to foster and protect the integrity of scientific research. Equally, I believe that it is our responsibility to provide comprehensive guidance and leadership for institutions, and to be assured that appropriate procedures have been adopted. Together the research community and all its components must take responsibility to maintain the quality and integrity of the research carried on in the United States.



## WELCOMING REMARKS\*

By

James B. Wyngaarden, M.D.\*\*

It is a great pleasure for me to extend an official welcome from the National Institutes of Health to each of you. We are delighted that the 2nd International Conference on Preventive Cardiology is meeting in Washington, and your meeting nearby has made it possible for the NIH to participate as host to one of the important sessions of the conference.

During this afternoon's program Dr. Claude Lenfant and his associates in the National Heart, Lung, and Blood Institute will tell you of the many ways in which the lessons that have been learned from research have been translated into effective messages for disease prevention and health promotion. These messages call for action, and in fact have been successful in triggering action by practicing physicians, other health professionals, and most importantly by members of the general public--all to the improvement of health. In many instances the innovative use of different channels of communication has been critical to the success the programs have enjoyed.

I believe that you will find the presentations of more than passing interest, for they distill the fruits of extensive experience in technology transfer--the activity that translates the results of biomedical research into better means for the prevention, care and cure of disease and disability. Of these three desired results, prevention is paramount. NIH has long been involved in prevention-related research, even though these activities might not always have been termed "prevention."

My immediate predecessor as NIH Director, Dr. Donald S. Fredrickson--well known to many of you--made a statement to the Congress in 1979 that in a few words describes the vital relationship between biomedical research and disease prevention. In speaking of the mission and function of the NIH, he said, "Our product is knowledge, fundamental knowledge, knowledge about life, disease and malfunction. And our ultimate aim, the aim of all that research, is prevention, because that clearly is the most useful extension of knowledge in the field of health."<sup>1</sup>

The NIH conducts comprehensive education programs aimed at the prevention or reduction of the three major cardiovascular and pulmonary risk factors: high blood pressure, high blood cholesterol, and cigarette smoking. The National High Blood Pressure Education Program was established in 1972.

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\*Presented at symposium on "Preventive Cardiology: From Research to Application--Making Technology Transfer Work," Masur Auditorium, June 20, 1989.

\*\*Director, National Institutes of Health, Bethesda, Maryland



Since 1972 physician visits for hypertension have increased by more than 64 percent, and the proportion of hypertensives who are controlling their blood pressure has almost tripled. Mortality from cardiovascular disease has declined steadily. Since 1972 age adjusted stroke mortality has dropped 54 percent. Coronary heart disease deaths have also declined 42 percent during the past 15 years. In contrast, deaths from non-cardiovascular diseases fell by only 10 percent.

It is reasonable to assume that the National High Blood Pressure Program must have had a substantial and beneficial impact on American health.

Based on the success of the High Blood Pressure Program and the results of biomedical research related to high blood cholesterol and cigarette smoking, the National Cholesterol Education Program and the Smoking Education Program were launched in 1985. Each of these education programs operate on the model of developing strong scientific foundations, building partnerships, and using networks of public and private-sector groups to help plan program strategies and employ many different communications channels to convey, repeat, and reinforce messages to professional and lay audiences.

As we consider how we can improve the translation and communication of the vital information flowing from research, we must always bear in mind that the source is biomedical research. In Lewis Thomas' words, "If biomedical research were allowed to languish, we would be required to 'make do' with today's information about human disease." Our agencies for public health, he said, "would be able to make only a marginal contribution to the prevention of alleviation of the illnesses contributing the most to premature death or disability, for the simple reason that we do not understand their causes, the underlying mechanisms by which they run their course, or in most instances how to prevent or cure them."<sup>2</sup>

Again, it is my privilege to welcome you to the National Institutes of Health.

#### REFERENCES

<sup>1</sup>Fredrickson, U.S. Congress, House, Committee on Interstate and Foreign Commerce: Future Directions, Hearings before the Subcommittee on Health and the Environment. 96th Congress, First Session, 1979, p. 92.

<sup>2</sup>Thomas, Lewis, "Biomedical Research and the Future of Public Health," in Health Affairs, Project Hope, Millwood, Va., Winter 1983.

REMARKS\*

By

James B. Wyngaarden, M.D.\*\*

The primary purpose of this ceremony is to give public recognition for the qualities and actions exemplified by our honorees. But in carrying out this pleasant function we also put on display the range of activities and talents required to make NIH work. Taken together the citations that appear in the program booklet form an impressionistic and colorful portrait of current NIH activities.

If time permitted, it would be interesting and, in fact, inspiring to go beyond the limited language of the citations to the remarkable activities for which the individual awards are being made. This year, as in years past, the awards attest to the sense of purpose, the dedication and the expertise shown by NIH personnel across the occupational spectrum, and in a great diversity of critically important activities. The proceedings of this and previous award ceremonies are rich with instances of how under differing circumstances individual colleagues or groups of our fellow workers have responded successfully to unusual challenges in such a way as to bring credit to the agency as a whole.

Each year as I have reviewed the award nominations I have been impressed by the variety of the accomplishments being honored.

For example, at the first awards ceremony after I became Director, special commendation was given for the way in which NIH personnel dealt with the effects of a near-blizzard--a subject that seems more refreshing than threatening when remembered on the first day of summer. At that time we expressed appreciation to the Clinical Center staff who assured uninterrupted patient care; to the grounds maintenance and housekeeping staffs who cleared and kept clear our walks and roads; to the GSI cafeteria employees who stayed in Building 10 to feed the staff over a snowbound weekend; to the police and firemen who helped stranded motorists; and to the maintenance engineers who stayed on their jobs long after their shifts had ended.

This kind of performance calls to mind the discipline and professionalism exhibited by the NIH police during the animal activist demonstrations on campus in the spring of 1988 and again this year. The steady competence of our police prevented a dangerous and destructive situation from escalating while protecting the basic rights of all.

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\*Presented at the NIH Director's Award Ceremony, June 21, 1989.

\*\*Director, National Institutes of Health, Bethesda, Maryland.

Permit me to mention one more illustration of the diversity of activities for which the Director's awards are given. This example is from the current year's honorees.

Shortly an award is to be made to a group from the Office of Science Policy and Legislation for its skill and sensitivity in managing the meetings of the Human Fetal Tissue Transplantation Panel and overseeing the development and distribution of its report. I need not tell you that the Panel was considering a highly charged issue in public meetings attended by an unusually large number of reporters. It was a situation calling for meticulous planning and careful management by our staff, where a host of large and small judgements had to be made on the spot--many with real potential for causing serious public misunderstanding, embarrassment, or controversy--but the challenge was met, smoothly and successfully.

There are many other examples of activities and services by NIH personnel to be honored today that are equally as worthy of attention and appreciation.

In today's ceremonies it will be my privilege to present awards in each of four different categories. These are the NIH Director's Award, the Outstanding Service Medal for members of the PHS Commissioned Corps, and two special awards for Equal Opportunity Achievement.

One of the latter category--the Harvey J. Bullock Jr. Award for Equal Opportunity Achievement--is given to recognize specific individual efforts in furthering equal opportunity by persons who are not EEO program leaders. The NIH Equal Employment Opportunity Award of the year is given to the person selected NIH-wide from those who during the year have received cash awards from the organizational component in which they are employed.

The PHS Outstanding Service Medal is presented to officers who have demonstrated outstanding continuous leadership in carrying out the mission of the PHS, or have performed a single accomplishment that has had a major effect on the health of the nation.

The NIH Director's Award is relatively new, having been established by my predecessor, NIH Director Donald S. Fredrickson. The award is designed to recognize exceptional performance in the Civil Service as well as in the Commissioned Corps. On occasion, the Director's Award may be given to persons outside the NIH who have made substantial or exceptional contributions to the benefit of our programs or people. I am delighted that today it will be my privilege to make an award to Dr. George Cahill, Jr. in recognition of his uniquely effective role in the development of the highly successful Howard Hughes-NIH Medical Students Research Scholars Program.

The 54 awards being given today provide recognition to only a minor fraction of the activities and accomplishments of the past year that are deserving of such honors, but they are representative of the qualities of dedication and excellence that make the NIH community what it is. I extend my heartiest congratulations to each honoree and to their friends and family members who are in attendance here.

This is not the time for me to make a valedictory statement to NIH as a whole. However, I am grateful to have the opportunity to express one thought to this convocation of honorees, their families and friends, together with the principal officers of NIH. I want to say what an honor and pleasure it has been for me to work side by side with you, and to experience with you the pride that comes from being a part of this remarkable community.





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STATEMENT BY

DR. JAMES B. WYNGAARDEN, M.D.

DIRECTOR

NATIONAL INSTITUTES OF HEALTH

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SENATE COMMITTEE ON LABOR AND HUMAN RESOURCES

JULY 24, 1989

Mr. Chairman and Members of the Committee:

I appreciate the opportunity to address the Committee and present my views on the problems the National Institutes of Health faces in recruiting and retaining senior scientists.

As an agency of the Department of Health and Human Services, Public Health Service, the NIH is the Federal focal point for biomedical research. Our mission at the NIH, where we have the preponderance of the responsibility for biomedical research, is to discover new knowledge that will lead to better health for everyone. NIH works toward this mission by: conducting research in its own laboratories; supporting the biomedical research of non-Federal scientists in universities, medical schools, hospitals, and research institutions throughout the country and abroad; assisting in the training of research investigators; and fostering and supporting biomedical communications.

NIH has become the world's premier biomedical research institution because of the consistently superior quality of its senior staff, who have made significant contributions to the major advances in the biomedical sciences and biotechnology over the last century. Within the last two decades, many of these advances have opened potentially valuable and lucrative

commercial applications and have caused a dramatic increase in the competition for top caliber senior researchers and science managers in both the private and academic sectors. Federal compensation for these employees has not kept pace with the increased competition. As a result, NIH has been experiencing severe problems recruiting and retaining senior level personnel of the prominence and stature required to lead and conduct National research programs into the causes and treatment of major human afflictions.

There are currently 176 highly qualified and talented members of the Senior Executive Service at NIH. Of these, 53 are physicians, and 104 have Ph.D. or other doctorate degrees. Nineteen hold other important senior level positions, including resource and facility management. Virtually all of these individuals can command substantially higher salaries in the private or academic sectors, and many are considering employment offers. All have been experiencing severe salary limitations over the last several years.

Our studies show that on the average, NIH Senior Executive Service physicians are paid about half as much as their academic counterparts. Other NIH doctoral staff who belong to the Senior Executive Service are paid 19 percent less than comparable positions in research-intensive universities. Furthermore, the



gap in compensation between the NIH and American medical schools is increasing. In 1982, our medical officers who were in the SES were paid \$39,000 less than their counterparts in American medical schools. Today that gap has widened to \$99,000. Many of our senior scientists are considering whether to remain with NIH because of these salary considerations.

Our situation can best be illustrated by the results obtained from a survey NIH recently conducted of employment offers that have been made to our permanent scientific staff within the last two years. Approximately one quarter of our permanent doctoral level scientists and science managers responded to this survey. Of the senior physicians who responded, 83 percent reported receiving one or more offers ranging from \$100,000 to \$500,000. The average employment offer was \$166,000; approximately twice what they are making at NIH. Among senior non-physician doctoral staff, 54% received employment offers of at least \$10,000 more than their NIH salary. The average offer was \$105,000, which is 50 percent higher than they are now earning. With offers of this magnitude, NIH can expect to lose a substantial number of key senior research scientists and science managers.

I share Mr. McFee's pleasure with President Bush's recent proposal, "The Senior Executive Salary Act of 1989," which would provide higher salaries to employees in positions requiring specialized and critical skills and an 8-25 percent raise for Senior Executive Branch officials generally.

The compensation gap has also made recruitment exceptionally difficult. For example, since 1980 NIH has not been able to recruit a single research scientist into the Senior Executive Service from the private or academic sectors to engage in the independent conduct of a clinical or basic biomedical research program. In 1980, NIH had 108 intramural research scientists in the SES. Since then, we have had 61 vacancies, and have been able to fill only 30, all from within the Government. This is not an optimal situation. To assure fresh leadership and innovation, we need to be able to hire scientists from outside of the Government. In addition, there are numerous cases of top candidates who, after expressing substantial interest in senior positions at NIH, withdrew from consideration because we could not offer an adequate salary or benefits. Among these, a large number of prominent candidates for five different Institute Director positions declined further consideration because NIH could not match their current salaries and benefits. During this same period of time, over twenty prestigious senior scientists expressed interest in positions for which NIH was recruiting. All declined further consideration because they were currently earning salaries ranging from 20 to 263 percent more than NIH could pay.

During the last year, NIH has also attempted to recruit such senior staff as: a pharmacologist to conduct AIDS related drug

analysis studies; a scientist to undertake research in nerve regeneration; a cancer radiation therapist; and several physicians in a variety of much needed surgical specialties, including general cancer, and thoracic and neurosurgery. NIH was not successful in filling any of these positions owing to inadequate compensation. As a result, a number of promising laboratory and clinical research initiatives have not been pursued, and several other existing programs have been curtailed. While this may not preclude research in these areas by other organizations, the cumulative loss undermines the overall strength of the NIH.

It is not difficult to understand how these salary differentials with the private sector also affect our ability to retain senior staff. While many senior staff remain at NIH because of its fundamental mission and its unparalleled reputation for scientific excellence, recruiters from academia and industry make highly attractive offers to our senior staff that only too often are accepted.

In the last ten years, NIH has suffered a net loss of 28 percent of the 108 intramural research scientists who originally entered the Senior Executive Service. All left NIH to accept positions in academic institutions, industry, and independent research laboratories at salary increases ranging from 50 to 300 percent. In the last six years, NIH lost a Deputy Director and several

Institute Directors due in part to salary considerations. Recently, a number of prominent scientists have left NIH due in part to salary considerations. These losses include one of the country's foremost experts in breast cancer, and the individual responsible for managing a program which included a national network of cooperative groups which conduct clinical research on new treatments for cancer.

A recent independent study of the NIH intramural research programs conducted by the Institute of Medicine of the National Academy of Sciences confirms our findings. In this report, the Institute of Medicine states, "The reduction in the number of senior researchers, the increasing age of those remaining, the failure to successfully recruit from outside, and the evidence of generally noncompetitive salaries justifies NIH concerns about their future ability to recruit and retain senior researchers and research administrators. This is particularly serious since many of the current researchers are approaching retirement age."

One of the Institute's recommendations was that "Congress authorize NIH to develop and implement a personnel demonstration project tailored to overcome the deficiencies of the current system." The Institute of Medicine suggested that the plan feature simplified hiring, classification, and pay administration, similar to the demonstration project now being conducted by the National Institute of Standards and Technology.



The Institute of Medicine also recommended an occupation-specific pay standard, based on surveys of market comparability; the ability to exceed Federal pay ceilings in justifiable circumstances; portability of retirement benefits between non-Federal employment and the NIH; and a limit on personnel services costs, in lieu of employment ceilings, as a way of controlling personnel costs.

Equally important is the adverse effect an inadequate pay scale has had on our junior and mid-level scientists. NIH is relatively successful in recruiting and developing bright and promising post-doctoral research scientists. Our employment trends indicate that as these scientists progress and begin to encounter salary compression due to pay limitations in the senior ranks, they leave the Government just as they are entering the peak of their careers. For example, within the last year, salary considerations have led several prominent mid-level scientists to leave NIH, including physicians specializing in Oncology, Pathology, Neurology, Dermatology, and Critical Care Medicine. NIH encourages this to some degree because it fosters cross-fertilization of ideas between NIH and the academic community, and allows NIH to bring in a new cadre of young bright scientists with fresh ideas. However, we expect that a continued limitation on the pay of senior level staff may accelerate this trend. If this occurs, NIH will have fewer available well trained mid-level researchers to advance to senior leadership positions.

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My views also are supported by the recent report of the National Commission on the Public Service. The Commission sounded an alarm that the noncompetitive salaries of the Senior Executive Service are undermining the Government's vital science programs. The report warned that the failure to increase these salaries will substantially diminish the ability to recruit and retain the highest quality biomedical researchers, engineers, and other senior career executives who manage essential services in the Government. The report suggests that the urgency of raises for career Senior Executives may be even more critical than salaries for elected and politically appointed officials. The Commission recommended "prompt action by the President and Congress to raise the cap on the Senior Executive Service, even if this means that their pay in some instances could exceed that being received by the political appointees above them."

NIH offers advantages that for many researchers have offset the salary differential. These include the intellectual stimulation and prestige of being a part of NIH, scientific freedom to choose their own research pursuits, access to state-of-the-art equipment, freedom from administrative and teaching responsibilities, and opportunities for rewarding associations with outstanding scientists within many disciplines. Some opportunities also exist for consulting, although they are subject to restrictions, and very few NIH employees earn the

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maximum of \$25,000 per year. However, in the face of the widening salary gap, these advantages become less compelling.

Our recruitment and retention difficulties are occurring at a time of great challenge and opportunity in the biomedical sciences. If NIH is to meet this challenge, it is vital that we have a core of top caliber senior researchers and science managers who will provide the necessary innovation and leadership. To do so, NIH must have the flexibility and capacity to compete nationwide for the best available scientific talent. In the closing remarks of its report, the Institute of Medicine stated "that personnel problems, both those relating to compensation and the overall personnel system, are compromising the ability of NIH to recruit and retain scientists of the highest quality." I firmly believe that a resolution to these problems is essential to restoring NIH to a fully competitive posture and demonstrating the commitment of the Federal Government to maintaining a first-class biomedical research program.

Mr. Chairman, this concludes my prepared statement. I would be pleased to answer any questions that you or other members of the Committee may have.

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